4th Edition

Nutritional Management of Renal Disease

Edited by
Joel D. Kopple
Shaul G. Massry
Kamyar Kalantar-Zadeh
Denis Fouque

NUTRITIONAL MANAGEMENT OF RENAL DISEASE

FOURTH EDITION

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Dedication

Joel D. Kopple
To my wife: Madelynn Kopple
To our children: David and Robin Kopple, Michael and Yael Kopple,
Deborah and Yury Nedelin, and Joshua and Calanit Kopple
To our Grandchildren: Ellis, Tabitha and Maxwell Kopple, Levi, Liora, Tamara and David Ariel Kopple, Elisheva, Chavah, Isaac and Theodore Nedelin, and Yeshaya, Eliyahu, Chaya Sarah, Batsheva, Yocheved, and Yehudis Kopple,
and to Jeffrey Alan Kopple

Shaul G. Massry
To my wife: Meira Massry
To our children: Efrat and Ram Cogan, Dr. Guy Massry, Yael and Geoffrey Rendon,
and Dr. Dina and Dr. Kenneth Grudko
To our grandchildren: Emma and Raef Cogan, Alexis Massry, Maya and Joseph Rendon,
and Ava and Sam Grudko

Kamyar Kalantar-Zadeh
To my wife: Dr. Grace-Hyunjoo Lee
To our children: Sara-Soojung, Diana-Sunhee, and Hannah-Soyeon

Denis Fouque
To my wife: Dr. Pascale Fouque
To our children: Camille and Rudy-Alexandre, Sarah and Alexandre, and Juliette and Alice
To our grandchildren: Jules and Romane

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Preface

We are pleased to present the fourth edition of *Nutritional Management of Renal Disease*. We believe this to be the most comprehensive of the four editions. Our goals for developing these books were to create both a key reference source of scholarly information and also a practical manual for the nutritional and metabolic management of people with or at increased risk for developing chronic kidney disease (CKD), kidney failure, or acute kidney injury (AKI). This book is designed for physicians, scientists, dietitians, nurses, students, teachers, and other workers in the fields of nutritional biology and nutritional healthcare.

Topics covered in the book's 53 chapters include the altered metabolism of nutrients in people with moderate or advanced CKD or AKI, the causes, prognostic implications, and methods of prevention and treatment of protein-energy wasting and frailty, nutritional risk factors for CKD, and the use of nutrition to prevent or treat progression of CKD and the uremic syndrome. The metabolism and endocrinology of divalent ions and bone mineral disorders in kidney disease are extensively discussed. Also covered in this book are treatment of anorexia, methods and effects of enteral, intravenous and dialytic nutrition, drug nutrient interactions, and the use of anabolic agents, physical conditioning and exercise training in CKD patients. State of the art information is presented on each of these subjects. Much effort was also given to provide practical information on the nutritional and metabolic management of kidney disease and kidney failure. The recently published KDOQI Clinical Practice Guidelines for Nutrition in CKD are extensively alluded to in the relevant chapters.

Although the four of us served as the editors, in a very real sense, the main and key contributors to this book, and the ones to whom any accolades should be given are the chapter authors. Most of the chapter authors were not the book editors, and we would like to acknowledge the tremendous amount of work and dedication that these individuals collectively have contributed to this compendium. These authors were invited to write chapters because they are virtually all authorities in their respective fields. These were the individuals who extensively reviewed the literature, often adding their own research and personal experience to the subject matter, and then summarized the information, basing their recommendations on an amalgam of the current state of the art admixed with their own experience and expertise. We express our gratitude and admiration to all of these contributors to the book.

Joel D. Kopple,
Shaul G. Massry,
Kamyar Kalantar-Zadeh and
Denis Fouque

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PART I

Normal and altered metabolism of chronic kidney disease

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CHAPTER

1

The KDOQI Clinical Practice Guidelines for Nutrition in CKD: 2020 update

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Introduction

Clinical practice guidelines are statements that include recommendations intended to optimize patient care that are informed by a systematic review of evidence and an assessment of the benefits and harms of alternative care options. Rather than dictating a one-size-fits-all approach to patient care, clinical practice guidelines offer an evaluation of the quality of the relevant scientific literature and an assessment of the likely benefits and harms of a treatment. This information enables health care providers to proceed accordingly, selecting the best care for a unique patient based on his or her preferences [1].

The original Clinical Practice Guidelines for Nutrition in Chronic Renal Failure by the National Kidney Foundation (NKF) Disease Outcomes Quality Initiative (KDOQI) was published in 2000 and provided in-depth information and recommendations regarding the several nutrition-related aspects of chronic kidney disease (CKD) [2]. Since then, there has been a remarkable increase in studies with focus on nutrition assessment and management of CKD. Moreover, the methodology for Clinical Guidelines development has also changed considerably. Therefore an update of the original guideline was timely and necessary. The KDOQI Clinical Practice Guideline for Nutrition in CKD: 2020 Update was developed as a joint effort by the NKF and the Academy of Nutrition and Dietetics (AND). In this chapter we will provide an overview of the process regarding guideline development and a concise description of the recommendations.

The guideline development process

The guideline development process involved multiple groups, primarily the NKF and AND, and the select members of the International Society of Renal Nutrition and Metabolism (ISRNM) who provided a critical review of the document. A work group was formed with members chosen through an application and review process considering the expertise in the diverse fields of nutrition in CKD and with special attention to include members from different countries to have representatives from each continent. The work group members consisted of physicians, registered dietitians or nutritionists, researchers, and methodological experts.

The steps in the guideline development process included selection of topics; determination of the scope of the topic; review of the evidence for clinical recommendations; and development, review, and approval of the recommendations.

The focus of the updated guideline defined by the work group members comprised of adults aged 19 years and older, CKD stages 1 through 5, including patients on maintenance dialysis and patients with a functioning kidney transplant. Three main areas were covered: macronutrients (including nutritional assessment), micronutrients and electrolytes, and other nutrients. Given the scope of the project and need for timeliness, the literature search was restricted to studies published between 1985 and 2017. Fig. 1.1 summarizes the steps followed to conduct comprehensive systematic reviews and how the findings from the systematic reviews were used to develop the guidelines according to the Standards for Developing

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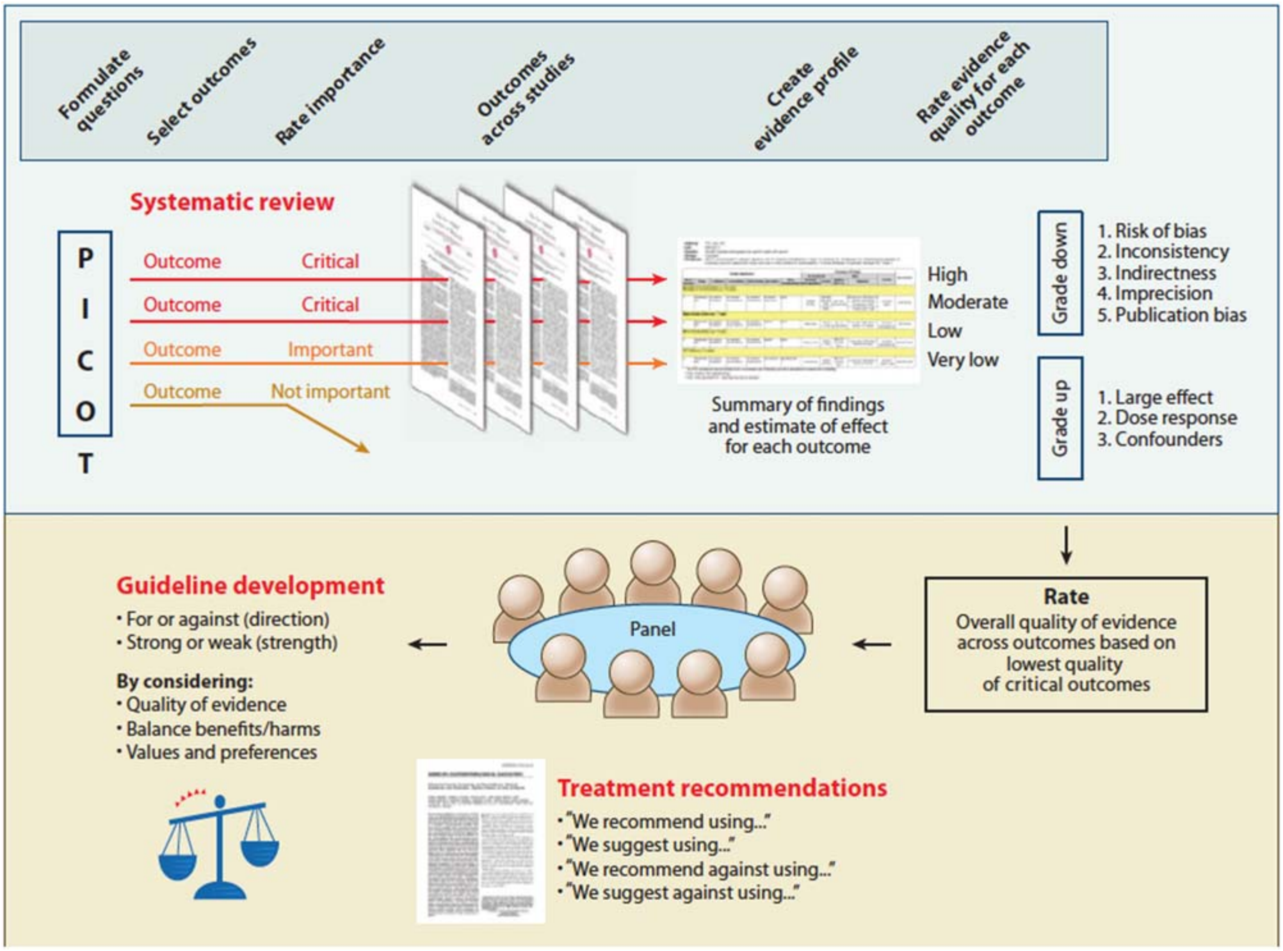
Formulate questions
Select outcomes
Rate importance
Outcomes across studies
Create evidence profile
Rate evidence quality for each outcome
Systematic review
P
I
C
O
T
Outcome
Critical
Outcome
Critical
Outcome
Important
Outcome
Not important
High
Moderate
Low
Very low
Summary of findings and estimate of effect for each outcome
Grade down
1. Risk of bias
2. Inconsistency
3. Indirectness
4. Imprecision
5. Publication bias
Grade up
1. Large effect
2. Dose response
3. Confounders
Rate
Overall quality of evidence across outcomes based on lowest quality of critical outcomes
Panel
Guideline development
• For or against (direction)
• Strong or weak (strength)
By considering:
• Quality of evidence
• Balance benefits/harms
• Values and preferences
Treatment recommendations
• "We recommend using..."
• "We suggest using..."
• "We recommend against using..."
• "We suggest against using..."

FIGURE 1.1 Schematic representation of the systematic review steps to inform guideline development panels. *Reprinted with permission from Falck-Ytter Y, Schünemann H.* AHRQ Annual Meeting 2009: "Research to Reform: Achieving Health System Change" September 14, 2009. *Available from: https://archive.ahrq.gov/news/events/conference/2009/falck-ytter-schunemann/index.html. [Accessed 06 May 2020].*

Trustworthy Clinical Practice Guidelines as stated by the National Academy of Medicine [1].

Approximately 100 questions covering both assessment and intervention of the three subtopics were proposed by the work group. The key questions used for evidence review are listed in the Guideline document [3]. For assessment questions, only studies that tested the validity, reliability, or relationship of an assessment tool against a comparative tool or mortality were included in the review. For intervention questions, only randomized controlled trials with a comparator and which had at least six individuals per arm were included. The main outcomes defined were mortality, comorbid conditions, CKD progression, quality of life, nutritional parameters, and nutrient biomarkers.

The first literature search focused on assessment and intervention questions identified 4857 and 11,017 potential studies, respectively. After applying the inclusion and exclusion criteria, 125 studies met the inclusion criteria for assessment questions and 225 studies met the criteria for the intervention questions. Relevant data were extracted from the included articles using a standardized data extraction tool. All included studies were critically appraised for risk of bias. Descriptive synthesis of evidence was conducted for all identified outcomes for which there were included studies. The review results were then provided for the work group members in three formats: (1) evidence summary, (2) study characteristics, and (3) quality of evidence. Each of the conclusion statements was assigned a GRADE (Grading of Recommendations, Assessment, Development, and Evaluations) to reflect the quality of studies, inconsistency of results, imprecision, indirectness of the evidence, and publication bias [4]. Using this method, the evidence for each outcome of interest was graded as A (high), B (moderate), C (low), or D (very low). The work group members then translated the available evidence into action statements and rated the strength of the recommendation. The grade for strength of recommendation was assigned Level 1 or Level 2.

This rating reflects the extent to which one is confident that the desirable effect of an intervention outweighed undesirable effects. Level 1 recommendation uses the terminology "We recommend" which means that this course of action should be applied to most people and practitioners can have confidence that implementing this recommendation has more benefit than risk. Level 2 recommendations use the terminology "We suggest."

It is important to point out with regard to the level of strength of the recommendation that a number of factors besides the quality of evidence are taken into consideration, including patient values and preferences, benefits and harms, cost and resources to implement the recommendation, acceptability, feasibility, and health equity. In addition to evidence-based recommendations, in certain scenarios "Opinion" statements were developed. These statements were created when there was not enough evidence or the evidence was of too low a quality to write a graded recommendation, but the work group determined it was important to provide some guidance to patients and practitioners. These recommendations are ungraded and usually refer to general or routine practice.

The recommendation statements were reviewed and edited several times until approved by the work group and incorporated into the final guideline.

For each recommendation statement, supporting materials are provided in the guideline including the following sections: rationale, detailed justification (evidence summary), special discussions, implementation consideration, and future research needs. Additional important references were provided for the discussion of the respective topic to include studies published after the final date of the literature searches. The final step was the peer review process. An internal review was conducted by KDOQI leadership, and after incorporating the reviewed points as appropriate an external review was conducted by experts in the field. The final step was an open public review.

Key points addressed in the 2020 updated guideline

The updated guideline statements focus on six primary areas: nutritional assessment, medical nutrition therapy (MNT), dietary protein and energy intake, nutritional supplementation, micronutrients, and electrolytes. Table 1.1 shows a summary of the statement topics covered in each primary area. In relation to the 2000

TABLE 1.1 Summary of the statements covered in the KDOQI Clinical Practice Guideline for Nutrition in CKD: 2020 Update (3).

	Statements
Guideline 1: *Nutrition assessment*	– Usual care – Technical devices and anthropometric measurement of body composition – Assessment with laboratory measurements – Handgrip strength – Methods to assess energy requirements – Composite nutritional indices – Tools/methods to assess protein and calorie intake
Guideline 2: *Medical nutrition therapy*	Medical Nutrition Therapy
Guideline 3: *Protein and energy intake*	– Energy intake – Protein amount – Protein type – Dietary patterns
Guideline 4: *Nutritional supplementation*	– Oral, enteral, and intradialytic parenteral nutrition – Dialysate nutrition supplementation – Long-chain omega-3 polyunsaturated fatty acids
Guideline 5: *Micronutrients*	– Micronutrient assessment – Folic acid – Vitamin C (Ascorbic acid) – Vitamin D – Vitamins E and A – Vitamin K – Trace minerals—selenium and zinc
Guideline 6: *Electrolytes*	– Acid load – Calcium – Phosphorus – Potassium – Sodium

guideline the current guideline provides a substantial incremental value in the topics that are covered.

The recommendations for nutrition assessment have been greatly expanded including new methods and tools to assess nutrition status and body composition, such as bioelectrical impedance, handgrip strength, conicity index, malnutrition inflammation score, and methods to measure or to estimate energy expenditure. Together with the recommendations on traditional anthropometric parameters, a detailed discussion concerning the accuracy, validity, and limitations of each method and tool is provided to support practitioners with their appropriate use in multiple scenarios. The need for further research in this area is critically important, especially in terms of development of risk prediction models using multiple nutritional markers, determining the effects of various nutritional interventions on nutritional markers, and whether changes in values of a nutritional marker correlate with outcomes as a marker of efficacy.

A new topic included in the 2020 guideline is the recommendation for MNT [5]. The recommendation emphasizes the importance of providing this collaborative approach by the health care team to optimize the nutritional care by tailoring it to the individuals' needs, nutritional status, and comorbid conditions.

Due to the expansion of well-designed studies on the impact of dietary protein intake on various outcomes in patients with CKD over the last two decades [6], a high level of evidence for recommendations for dietary protein intake has been achieved. More specifically, the updated guidelines provide recommendations for protein restriction (with or without ketoacid analogs) in appropriate patients with CKD to reduce the risk of initiation of renal replacement therapy and death. It is noted, however, that there is a significant need for future appropriately designed clinical trials to investigate the effects of very low protein diets and protein type (vegetable vs animal) on important CKD-related clinical outcomes.

In recent years, emerging evidence has indicated that overall eating patterns, instead of individual nutrients, maybe a better predictor of outcomes in CKD [7,8]. Recommendations regarding the Mediterranean diet and a dietary pattern with increased intake of fruits and vegetables are discussed in the guidelines and the need for future studies to examine their potential impact is further highlighted.

Protein-energy wasting (PEW) is still highly prevalent in advanced CKD patients, and treatment of this condition continues to be challenging for the health care team [3,9,10]. Detailed and comprehensive recommendations addressing different types and routes of nutritional supplementation in the face of PEW are provided in the newly updated guidelines. Notably, strategies to prevent dialysis-induced catabolism and interventions to treat PEW in patients with CKD stages 3–5 and maintenance dialysis patients are presented in detail. Nevertheless, several important considerations regarding prevention and treatment of PEW, such as who to treat (all patients vs the higher risk individuals), when to administer supplements (e.g., immediately before or during dialysis treatments vs during the interdialytic interval), how much and for how long to administer, and how to monitor the response are not covered by the current guidelines and require further research.

The inclusion of micronutrient (vitamins and trace elements) recommendations represents an important advance in the updated guidelines. However, provision of accurate and reliable evidence-based statements for assessment and administration of micronutrients in patients with CKD remains challenging. Despite the large number of trials on the effects of micronutrients supplementation, most of them do not report the baseline status of the micronutrients examined or the dietary intake during the studies; this has led to significant limitations in the evidence-based recommendations. Furthermore, differences in published studies regarding the doses of the supplements, duration of the intervention and the outcomes analyzed, among several other issues, make it difficult to provide recommendations on the amounts of micronutrients to be given and the types of CKD patients who should receive these supplements. Taking all these issues into consideration, the work group agreed to develop opinion-based recommendation to guide practitioners and to emphasize the need to individualize micronutrient supplementation.

The last set of guidelines is dedicated to electrolyte recommendations. It is well known that as CKD progresses and develops, disturbances in mineral metabolism and changes in acid–base homeostasis occur [11]. Therefore dietary control of electrolytes and net acid production are of paramount importance for the prevention and treatment of many of the complications of CKD. Although the level of evidence is still low, a statement on management of net acid production through increased intake of fruits and vegetables and its potential effect on reducing the decline of kidney function are provided along with detailed suggestions for future research. Regarding dietary phosphorus, besides the evidence for recommending adjustment in phosphorus intake to maintain normal serum phosphorus concentrations, the importance of recognizing the bioavailability of dietary phosphorus sources, with emphasis on phosphorus additives, is addressed. The guidelines also provide recommendations on dietary sodium and potassium intake based on the available evidence. Most importantly, the guidelines do not provide any recommendations related to pharmaceutical therapies for any of the electrolytes, since this was beyond the scope of the project.

Conclusion

The updated nutrition guidelines in CKD is a result of more than 5 years of work of multiple individuals and provides substantial information based on recent advancements in the care of patients with CKD. It is important to point out, however, that the guideline statements do not cover certain patient populations such as those who are obese, elderly, who have acute kidney injury. Nor do the guidelines address such interventions as exercise or any pharmacotherapies to prevent or treat nutritional abnormalities. The guidelines also do not stratify patients based on their ethnic or racial backgrounds, which could have obvious implications. Since the guideline updates are a continuous and dynamic process, these additional areas, with their significant clinical relevance, will be covered in the future.

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CHAPTER

2

The influence of kidney disease on protein and amino acid metabolism

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Introduction

Chronic kidney disease (CKD) is a progressive disorder that afflicts 15% of the US adults or over 30 million individuals [1]. The presence of CKD is characterized by metabolic abnormalities that result from the progressive accumulation of unexcreted toxins as kidney excretory capacity declines. As these metabolic processes worsen, patients develop the uremic syndrome, which is characterized by fatigue, loss of lean body mass, and a multitude of nonspecific symptoms. It is speculated that these nonspecific, uremic symptoms are generated by the accumulation of uremic toxins and these, in turn, are produced by the metabolism of protein and ultimately, amino acids. As kidney function is lost, increasingly severe uremic symptoms develop in association with the progressive accumulation of potential uremic toxins, such as, *p*-cresol, indoxyl sulfate, and products of the digestion of indoles. However, the assignment of specific uremic symptoms to the accumulation of a specific uremic toxin or group of toxins has not been accomplished. Instead, the circulating levels of uremic toxins in patients with CKD are associated with the development of inflammation, inhibition of wound repair, and the generation of cardiovascular disease in patients with CKD [2].

By far, the body's largest store of protein and amino acids is muscle, and it participates in the development of uremic symptoms because muscle protein can be degraded to amino acids and its metabolites. The characterization of protein turnover and of losses of muscle proteins was developed in large part by Rittenberg and Urey in 1939 [3]. They succeeded in generating a radioisotope of nitrogen (15N). Subsequently, Schoenheimer et al. reported that following the administration of 15N-labeled tyrosine to animals, only half of the label was excreted [4]. The rest of the label was incorporated into body proteins, confirming that proteins are in a dynamic state of synthesis and degradation. Reports of muscle turnover rates in humans revealed that adults degrade and synthesize roughly 3%−5% of the total amount of cellular proteins daily and that this process is highly selective. For example, in CKD there is impairment in intracellular signaling responses to insulin or insulin-like growth factor-I (IGF-I) resulting in muscle atrophy. There also are enhanced potential mediators of the processes of protein synthesis and degradation. For example, metabolic acidosis and increases in circulating angiotensin II or inflammatory cytokines levels can contribute to muscle wasting by stimulating the degradation of muscle proteins by the ubiquitin−proteasome pathway (UPS) [5,6]. It is well established that this is the major proteolytic system that degrades proteins in normal individuals and in patients with CKD [7]. Besides regulating protein turnover, muscle influences the intracellular stores of amino acids and specifically, the turnover of branched-chain amino acids (BCAA). This is relevant because BCAA are critical "building blocks" of muscle protein. Not surprisingly, certain factors that regulate muscle protein metabolism also regulate the turnover of BCAA. The development of metabolic acidosis activates the UPS to degrade muscle protein and at the same time, it activates branched-chain ketoacid dehydrogenase to degrade BCAA. Thus muscle metabolism is integrated with amino acid metabolism [8−10]. In this chapter, we will explore the roles of other

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mediators, including metabolic responses to myostatin, a negative regulator of muscle mass, and a critical mediator of muscle metabolic defects in CKD [11]. We address these responses because they provide insights into the pathophysiology of nutritional problems raised by CKD. Moreover, in patients with progressive CKD, attention to the evaluation and correction of nutritional factors can substantially ameliorate specific metabolic problems, including maintenance of protein stores and slowing of the loss of residual kidney function (i.e., progression of CKD). In this chapter, we will illustrate mechanisms that regulate the degradation of muscle proteins to peptides and amino acids and we will discuss how changes in protein metabolism influence the formation of metabolic disease and uremic toxicity.

Before reviewing changes in protein and amino acid turnover, we will briefly discuss factors that influence the development of uremia. First, the "intact nephron hypothesis" explains why monitoring the glomerular filtration rate (GFR) is necessary. The hypothesis deals with the finding that each kidney is composed of 0.75−1.25 million nephrons, and each of these nephrons functions as an independent unit [12,13]. The sum of remaining healthy nephrons in damaged kidneys provides a residual, "whole-kidney" GFR. Therefore the GFR of the damaged kidney provides a means of gauging the remaining physiologic and metabolic functions of the kidney (e.g., regulation of blood pressure and endocrine functions plus the concentrations of ions and the accumulation of unexcreted or undegraded metabolic waste products). In patients with diabetic nephropathy or other kidney diseases, the rate of decline in GFR is generally linear and hence can be measured as the rate of loss of kidney function if plotted as the reciprocal of serum creatinine or GFR estimated from serum creatinine or cystatin (eGFR). The relationship is linear in most patients without breakpoints related to acute kidney injury, providing an index of the rate of loss of whole-kidney GFR [14].

Influence of protein intake on CKD

In the first half of the 20th century, Thomas Addis introduced the concept of "osmotic work" [15]: rodents were fed diets containing varying amounts of protein, and those fed a high-protein diet developed renal hypertrophy and evidenced kidney damage and ultimately death. Although the contribution of an increased osmotic workload to progressive kidney damage has not been documented, subsequent investigators have determined that dietary protein loading resulted in increases in GFR and glomerular hypertension and ultimately induced progressive glomerulosclerosis.

Understanding how changes in protein metabolism influence uremic toxicity is important because once activated, mechanisms that create uremic toxins are not easily corrected. A potential intervention that slows the loss of kidney function in patients with CKD is to limit the amount of protein in the diet [16,17]. This strategy can effectively suppress uremic toxicity by at least three mechanisms: (1) nitrogen-containing uremic toxins and organic acids are derived from the catabolism of dietary and endogenous proteins. Consequently, the more protein in the diet, the greater amounts of amino acids that are available for the production of uremic toxins. (2) There is increasing evidence that the production of uremic toxins arises by the gastrointestinal microbiome leading to the ongoing loss of kidney function. For example, increasing dietary protein intake provides more substrates for the synthesis of uremic toxins in the intestinal microbiota. (3) Dietary manipulation to decrease the accumulation of uremic toxins is not limited to limiting dietary protein alone since diets that are rich in protein also contain an excess of potentially toxic inorganic ions, including sodium, phosphate, potassium, and hydrogen ion [18−20]. For example, increasing dietary protein intake can enhance the metabolism of amino acids and the degradation of some of these amino acids (e.g., sulfa-containing amino acids and ring-shaped amino acids, phenylalanine, tyrosine, and tryptophan metabolism leads to an increase in the production of acid that is poorly excreted because of the loss of kidney functions). In addition, increases in acid levels can stimulate muscle protein losses and increase the progression of muscle wasting.

Dietary restriction of protein

The original approach for determining specific metabolic targets was to examine the effect of changes in dietary protein and to measure nitrogen balance. The approach is used because it is a precise measure of the net balance between protein synthesis and protein degradation. Notably, the World Health Organization and and nutrition researchers have used it for more than 80 years dietary protein and amino acid requirements [21]. The minimum amount of high biological value protein intake within which protein homeostasis could be maintained is 0.36 g/kg per day, a level of protein intake that requires substantial metabolic adaptation to utilize the dietary protein maximally. However, a dietary level of 0.6 g/kg per day and the modification of the diet to increase the intake of primarily high biological value protein; using this level of dietary protein,

protein reserves are sustained in adults [22,23]. The delicate balance between protein synthesis and degradation determines the success of dietary management of CKD. Using this level of dietary protein ensures the goal of providing enough dietary protein to minimize the development of protein-energy wasting as well as avoiding toxicities arising from the ingestion of an excess of dietary protein.

The evidentiary record associated with an excess of dietary protein is persuasive: an increase in the production of uremic toxins and the accumulation of potentially toxic ions result directly from a level of protein intake above the minimum intake of dietary protein. It follows that successful restriction of dietary protein will be associated with both decreased production of uremic toxins and reduced accumulation of inorganic ions. Notably, dietary protein restriction is an established intervention used to prevent or reduce the symptoms of uremia in CKD patients. Unfortunately, the successful implementation of a low-protein diet is difficult and other factors affect renal outcomes. The difficulty in achieving compliance is a major outcome in publications assessing the outcomes of low-protein diets in patients with kidney disease (see Table 2.1) [20,24–40]. Successful implementation of a low-protein diet requires reliable measurements of protein intake plus regular monitoring to determine if patients being treated with low-protein diets are indeed receiving enough protein and other nutrients (e.g., energy) to maintain nitrogen balance. There are other factors to consider when determining nitrogen balance. For example, the rate of protein degradation has been found to be suppressed in muscles treated with the ketoacid, α-ketoisocaproate [41], [42]. This is relevant because very low-protein diets combined with nitrogen-free analogs of essential amino acids (i.e., ketoacids) have been shown to maintain nitrogen balance. Besides the amount of dietary protein, the nutritional adequacy of trace elements, minerals, and vitamins has not been established in patients with very low dietary protein plus supplements of essential amino acids or ketoacids. Fortunately, the safety and utility of these very low-protein targets in CKD have been tested repeatedly, and results indicate that a mixture containing sufficient amounts of precursors of essential amino acids from ketoacids and hydroxy acid analogs of essential amino acids are safe and reduce the accumulation of uremic toxins. This response improves protein stores and can delay the rate of CKD progression (see Chapter 16: Dietary Interventions to Slow the Progression of Chronic Kidney Disease and Improve Metabolic Control of Uremia).

As noted, the critical element required for maintaining protein stores in patients prescribed low-protein diets is to improve compliance to the dietary regimen. The classic report by Folin showed that the change in urea excretion is the principal response to the amount of protein consumed [43]. This relationship has been confirmed and provides the basis for monitoring compliance with low-protein diets [43–45]. The accuracy of this method of measuring nitrogen balance is mainly based on the daily urinary excretion of urea and specifically, a difference in the estimated excretion of all forms of nitrogen. The initial goal is to identify patients who have a change in dietary protein from the prescribed amount. The first step is to evaluate if body weight and the concentrations of blood urea nitrogen concentration are constant; if these values are unchanging, the patient can be considered to be in the steady state. The second step is to compare the prescribed amount of protein in the diet with the estimated amount of nitrogen excretion which is composed of three parts. Firstly, we measure the amount of urea nitrogen contained in a 24-hour urine collection. Secondly, urea nitrogen accumulated in the body can be calculated because urea nitrogen is distributed equally in body water (~ 60% body weight is designated as the amount of water in adult patients with CKD). Since the urea concentration is the same throughout body water, the accumulation of urea nitrogen following a change in the diet can be estimated mainly from the body water content or 60% of body weight multiplied by the blood urea nitrogen. Thirdly, other forms of excreted nitrogen (e.g., uric acid, creatinine, feces, etc.) can be calculated from an average nonurea nitrogen value that averages 0.031 g/kg/day. In summary, the patient's compliance with a prescribed dietary protein can be assessed by comparing the prescribed amount of dietary protein nitrogen with the calculated "output" of nitrogen (i.e., grams of urea nitrogen excretion) plus the amount of nonurea nitrogen excreted (i.e., 0.031 gN/kg body weight/day). If the amount of measured and calculated nitrogen excretion exceeds the amount of dietary protein nitrogen (protein is estimated to be 16% nitrogen), the patient should be evaluated by a dietician to determine how to adjust the amount of dietary protein that will achieve compliance.

Metabolic acidosis

The concept of the trade-off hypothesis was advanced by Neil Bricker and others to explain what occurs in patients who have intact responses to changes in the degree of kidney failure, including the development of metabolic acidosis [46]. The concepts developed by Bricker et al. were linked to their investigations that documented that patients with CKD undergo buffering of acid in their bones a response

TABLE 2.1 Notable dietary protein restriction studies.

Study	Date published	N	Design	Protein target (intervention group)	Control	Mean follow-up	Primary outcome	Intervention successful? ($P < .05$)
Rosman et al. [23]	1985	199	RCT	0.4–0.6 g/kg/d	Usual diet	24 months	CKD progression	Yes
Jungers et al. [24]	1987	19	RCT	0.4 g/kg/d + ketoanalogs	0.6 g/kg/d	12 months	Need for dialysis	Yes[a]
Rosman et al. [25]	1989	207	RCT	0.4–0.6 g/kg/d	Usual care	18 months	CKD progression	Yes
Locatelli et al. [26]	1991	456	RCT	0.6 g/kg/d	1 g/kg/d	2 years	CKD progression	No[b]
Williams et al. [27]	1991	95	RCT	0.6 g/kg/d	0.8 g/kg/d	19 months	CKD progression	No
D'Amico [28]	1994	128	RCT	0.6 g/kg/d	1 g/kg/d	27 months	CKD progression	Yes
Klahr et al. (MDRD Study I) [29]	1994	1585	RCT	0.58 g/kg/d	1.3 g/kg/d	2.2 years	CKD progression	Yes[c]
Levey et al. (MDRD Study II) [30]	1996	255	RCT	0.28 g/kg/d + ketoanalogs	0.58 g/kg/d	2.2 years	CKD progression	No
Malvy et al. [31]	1999	50	RCT	0.3 g/kg/d + ketoanalogs	0.65 g/kg/d	20 months	CKD progression	No
Hansen et al. [32]	2002	82	RCT	0.6 g/kg/d	Usual diet		CKD progression	Yes
Meloni et al. [33]	2002	69	RCT	0.6 g/kg/d	Usual diet	12 months	CKD progression	Yes
Prakesh et al. [34]	2004	18	RCT	0.3/kg/d + ketoanalogs	0.6 g/kg/d	9 months	CKD progression	Yes
Feiten et al. [35]	2005	24	RCT	0.3 g/kg/d + ketoanalogs	0.6 g/kg/d	4 MONTHS	CKD progression	No
Mirescu et al. [36]	2007	53	RCT	0.3 g/kg/d + ketoanalogs	0.6 g/kg/d	48 weeks	CKD progression	Yes
Cianciaruso et al. [37]	2009	423	RCT	0.55 g/kg/d	0.8 g/kg/d	7 years	Composite (dialysis + death)	No
Sanchez et al. [38]	2010	64	RCT	0.6 g/kg/d	1 g/kg/d	6 months	CKD progression	No
Jesudason et al. [39]	2013	65	RCT	50–70 g/d[a] (20% nutrient composition)	90–120 g/d[a] (30% nutrient composition)	12 months	CKD progression	No[d]
Garneata et al. [19]	2016	207	RCT	0.3/kg/d + ketoanalogs	0.6 g/kg/d	15 months	CKD progression	Yes

[a] *In low CrCl patients.*
[b] P < .06.
[c] *Among patients with GFR 25–55 mL/min/1.73 m^2.*
[d] *Significant in patients with GFR <120 mL/min/1.73 m^2.*
CKD, Chronic kidney disease.
RCT, Randomized control trialand.

that contributes to the development of uremic bone disease [47,48]. The specific concept was that increasing CKD led to the retention of more acid and this, in turn, worsened the degree of abnormal metabolic responses. Their reports provided at least two factors related to the acidosis that would contribute to the development of the bone disease: (1) an increase in the amount of dietary protein generates more acid; and the degree of renal insufficiency limits the excretion of acid arising from metabolism of proteins and amino acids. It was concluded that an excess in dietary protein increases the intake of sulfur-containing amino acids plus phosphorylated proteins and lipids. These substrates are metabolized to sulfuric and phosphoric acids and when CKD limits the excretion of acid which is by bicarbonates, intracellular buffers, and bone. Although these processes ameliorate the acidemia, the trade-off principle is that these patients develop more bone disease. These considerations can have clinical benefits. As an example, results from a randomized, controlled trial of oral bicarbonate therapy in chronic ambulatory peritoneal dialysis patients identified an increase in body weight and muscle mass plus fewer hospitalizations compared to patients who had higher alkali concentrations in their dialysate. [49]. Several other investigations have linked the development of acidosis to protein degradation and demonstrated the salutary effects of correcting acidosis in otherwise normal and CKD patients (Table 2.2) [28,49–60].

Not only does the successful treatment of metabolic acidosis suppress losses of protein mass in patients with CKD but it also has been reported that correcting acidosis can even slow the rate of loss of kidney function [55,61,62]. Besides these positive responses, treatment of metabolic acidosis can also suppress renal injury by blocking the tubulointerstitial inflammation arising from excess acid plus ammonia production with activation of complement and endothelin.

Evidence indicates that the metabolism of amino acids and proteins in the muscle is linked. For example, in skeletal muscles of rodent models of metabolic acidosis, there are parallel changes in the catabolism of protein and amino acids. These changes act in parallel because stimuli like metabolic acidosis stimulate muscle protein degradation by activating the UPS by complicated pathways that include stimulation of genetic

TABLE 2.2 Evidence that metabolic acidosis induces protein catabolism in children and CKD patients.

Subjects investigated	Measurements of effectiveness	Outcome of trial
Infants [32]	Low birth weight, acidotic infants were given $NaHCO_3$ or NaCl	$NaHCO_3$ supplement improved growth
Children [33] with chronic kidney disease (CKD)	Children with CKD had protein degradation measured	Protein loss was ~ twofold higher when HCO_3 was < 16 mM compared to > 22.6 mM
Normal adults [34]	Induced acidosis and measured amino acid and protein metabolism	Acidosis increased amino acid and protein degradation
Normal adults [35]	Induced acidosis and measured nitrogen balance and albumin synthesis	Acidosis induced negative nitrogen balance and suppressed albumin synthesis
CKD [36]	Nitrogen balance before and after treatment of acidosis	$NaHCO_3$ improved nitrogen balance
CKD [37]	Two years $NaHCO_3$ therapy versus standard care	Slowed loss of creatinine clearance and improved nutritional status
CKD [38]	Essential amino acid and protein degradation before and after treatment of acidosis	$NaHCO_3$ suppressed amino acid and protein degradation
CKD [39]	Muscle protein degradation and degree of acidosis	Proteolysis was proportional to acidosis and blood cortisol
CKD [40]	Nitrogen balance before and after treatment of acidosis	$NaHCO_3$ reduced urea production and nitrogen balance
Hemodialysis [41]	Protein degradation before and after treatment of acidosis	$NaHCO_3$ decreased protein degradation
Hemodialysis [42]	Serum albumin before and after treatment of acidosis	$NaHCO_3$ increased serum albumin
CAPD [43]	Protein degradation before and after treatment of acidosis	$NaHCO_3$ decreased protein degradation
CAPD [31]	Weight and muscle gain before and after treatment of acidosis	Raising dialysis buffer increased weight and muscle mass

CAPD, chronic ambulatory peritoneal dialysis.

components of the UPS [5–52]. In addition, Garibotto et al. have reported that intestinal BCAA absorption occurring after a meal involves nonessential amino acids and branched-chain ketoacid dehydrogenase [9,63]. The result leads to excessive catabolism of BCAA [10]. From these reports, we conclude that several factors, including metabolic acidosis, stimulate mechanisms of amino acid and protein degradation [64–66]. Interestingly, there also is a role for glucocorticoids in mediating muscle protein catabolism: it has been demonstrated that metabolic acidosis stimulates muscle protein breakdown only if there is a physiologic increase in glucocorticoid production [64,67].

Raising the amount of protein in the diet of patients with CKD will increase the intake of sulfa-containing amino acids (e.g., methionine, cysteine, and cysteine) as well as the intake of other acid amino acids and such as arginine, phosphoproteins, and phospholipids. Metabolism of these amino acids and phosphorylated compounds will generate acid, and when acid production exceeds the ability to excrete the acid, hydrogen ion exacerbates the complications of metabolic acidosis. This is easily detected by measuring the serum bicarbonate in patients with CKD: if the clearance is stable and the serum bicarbonate level is <22 mM, dietary protein is likely to be the culprit and dietary protein restriction should be curtained [68]. There are at least two other methods used to treat metabolic acidosis of CKD: (1) by increasing the amounts of fruits and vegetables in the diet to raise the intake of citrate to neutralize acid accumulation and (2) by administering $NaHCO_3$ or solutions of sodium citrate and citric acid [56,69].

Role of protein metabolism in hypertension

Estimates of the prevalence of stage 2 hypertension (>140/90mmHg) in patients with CKD exceed 60% [70]. Protein intake and metabolism are among factors that influence blood pressure by its association with the elasticity of blood vessel walls. In addition, patients with CKD are at increased risk for developing positive sodium balance. If CKD patients eat an excess amount of protein, they also will ingest ions and ion precursors. When the amounts of salt and other ions in the diet exceed the kidney's capacity to excrete them, the retention of inorganic ions will contribute to the development of hypertension.

Arginine has the potential to influence many physiologic processes because it is a major substrate for the synthesis of nitric oxide. For example, L-arginine supplements prevent the development of hypertensive nephrosclerosis in salt-sensitive Dahl/Rapp strain of rats [71,72]. In animal models of diabetic nephropathy, L-arginine supplements were found to ameliorate the degree of nephropathy and reduce the renal hypertrophy that is induced by a high-protein diet [73]. Finally, arginine supplements have improved renal function in rats with ureteral obstruction or puromycin aminonucleoside-induced nephrosis [74]. A longstanding stumbling block to the interpretation of these responses is the problem of the arginine paradox: it states that the beneficial effects of arginine supplements occur even though the intracellular arginine concentration is substantially above the Michaelis constant of nitric oxide synthase. Erez et al. found that intracellular nitric oxide synthase forms a complex with argininosuccinic lyase providing L-arginine as a substrate for nitric oxide synthase [75]. In healthy subjects, oral or intravenous administration of L-arginine causes diuresis and lowers blood pressure but changes GFR minimally; these changes can be associated with the development of microalbuminuria [76–79]. Taken together, dietary arginine could raise diuretic responses in fluid overload states, although this has not been rigorously tested. Caveats to the use of L-arginine are that in children with CKD, administration of arginine does not improve endothelial function [80].

Uremic toxins derived from protein metabolism

Pathophysiologic responses to ions that are associated with protein intakes >1.2 g protein/kg/day develop a constellation of problems in patients with CKD and uremia [81] (see Chapter 6: Uremic Toxins: An Integrated Overview of Classification and Pathobiology). There are at least three principal mechanisms of protein and amino acid metabolism that generate uremic toxicity. First, catabolism of dietary proteins, peptides, and amino acids occurs when proteases, amino acid oxidases, and gut bacteria degrade protein and amino acids. Second, metabolic processes mediated by gut bacteria can activate primary or secondary changes during the metabolism of protein, peptides, and amino acids [82]. In patients with CKD, the microbiome is altered by dietary factors as well as by impaired protein synthesis, frequent exposure to antibiotics, use of iron and phosphate binders. Many uremic toxins are produced by the fermentation of protein and amino acids by dysbiotic bacteria and are absorbed into circulation. The toxic compounds produced from protein metabolism include ammonia, thiols, phenols, indoles, and other solutes, and these changes could contribute to uremic symptoms (see Chapter 6: Uremic Toxins: An Integrated Overview of Classification and Pathobiology). Third, indirect pathways can produce toxic products from the metabolism of proteins, peptides, and amino acids that enter into the gut. Products of protein fermentation substrates in the gut can influence metabolic pathways, including insulin resistance and inflammation [83−86]. Although investigations into experimental and clinical consequences of metabolic changes caused by variations in the gastrointestinal microbiome have been partially defined, additional investigations are needed to document their role in the metabolism of protein and amino acids.

Examples of uremic toxins include *p*-cresol arising from the metabolism of phenol and indoxyl sulfate, a product of tryptophan metabolism. In patients with CKD, circulating levels of these tryptophan-derived compounds are associated with the presence of inflammation, the inhibition of wound repair, and abnormalities in vascular diseases [2]. Specifically, increased circulating levels of indoxyl sulfate or *p*-cresyl sulfate have been linked to CKD progression and cardiovascular morbidity and mortality [87−89]. The contribution of these compounds to uremic toxicity was formally tested by oral administration of a carbon adsorbent of indoxyl sulfate, AST-120, which is capable of blocking its absorption from the gastrointestinal tract. Several rodent-based studies have shown that AST-120 can slow down the CKD progression and improve the metabolism of CKD models. However, a large clinical trial conducted in the United States did not support the beneficial responses to treatment with AST-120 [90−92].

Homocysteine is an example of an amino acid metabolite of methionine. In adults without CKD, homocysteine has been linked to the acceleration of the development of atherosclerosis, and potentially an elevated homocysteine level may portend a poor prognosis in patients with coronary artery disease [93,94]. In CKD patients circulating homocysteine is found at high levels, but the mechanism for this result is unknown [95]. Presumably, high circulating levels of homocysteine arise from abnormalities in the metabolism of sulfur amino acids in CKD patients, but the biochemistry of impaired metabolism of sulfur-containing amino acids is unknown [96]. In healthy adults, the treatment for accelerated atherosclerosis occurring in association with a high homocysteine level is vitamin B6 plus folinic acid, but this therapy has not shown a clinically significant reduction in cardiovascular outcomes in CKD patients [97].

Excessive sodium

Salt is ubiquitous and is widely used, especially in the modern era, and has become a food preservative dedicated to enhance culinary flavor. Importantly, its consumption is correlated with protein intake. For patients with CKD, sodium chloride develops a critical metabolic response that is generated when kidney function is impaired. In dealing with salt intake, the trade-off hypothesis mentioned before is relevant. It refers to a CKD-stimulated activation of pathophysiologic responses that interfere with kidney functions. For example, patients with CKD initially develop sodium retention, which results in expansion of the extracellular volume and increases in body weight and blood pressure. These stimuli, however, trigger pathophysiological adaptions in the remaining tubules that impair tubular reabsorption of sodium. In this case, the trade-off for the CKD patient is the persistence of impaired tubular sodium reabsorption. For CKD patients, this response can create difficulties when there is an abrupt decrease in their salt intake. For example, if CKD patients who are in the steady state develop a sharp decrease in salt intake, the response of their kidneys will include a sluggish increase in their ability to raise the tubular reabsorption of sodium. The consequence will result in a net loss of sodium of both extracellular and intravascular volumes causing reduced perfusion of the kidneys and subsequently, a decrease in GFR [98]. On the other hand, a long-term decrease in salt intake appears to have beneficial effects on renal progression [99].

Proteinuria is a determinative factor in the progression of renal disease. High sodium intake in experimental models is associated with increased proteinuria and GFR decline. Furthermore, there is evidence that a high or even normal sodium intake may counteract the antiproteinuric effects of angiotensin-converting enzyme inhibitors (ACEi). Notably, in a reanalysis of the Ramipril Efficacy In Nephropathy (REIN) and REIN-2 trials, a high dietary sodium blunted the antiproteinuric impact of ACEi, an effect that is independent of blood pressure control [100]. An excessive sodium intake during the progression of CKD increases extracellular volume and contributes not only to elevated blood pressure, proteinuria, and progressive renal disease but also exacerbates cardiovascular disease [101]. Although not traditionally thought of as a uremic solute, salt should meet the criteria for one because it accumulates in CKD and is toxic in high amounts [102].

Phosphates

Phosphate meets the criteria for a uremic toxin because it accumulates in CKD and is toxic at high levels. The nature and degree of toxicity with phosphates are varied. Phosphates are minerals present in bone and are involved in a host of cellular processes. Specifically, organic phosphates are found in high amounts in protein sources—all meats, dairy products, and plant-based food such as beans and nuts. Moreover, they are frequently added to food as a preservative with high amounts present in packaged foods and many "dark" beverages. A report by Williams et al. revealed that dietary protein restriction will significantly decrease the urinary excretion of phosphates and others have reported that dietary protein restriction in advanced CKD is associated with lower requirements for phosphate binders [26,103].

In animal models of CKD, it has been shown that phosphate loading increased the rate of loss of kidney function (i.e., increased progression). Conversely, dietary phosphate restriction has been linked to responses that include prevention of proteinuria, kidney calcifications, histologic changes, functional deterioration, and death. Some of these findings were also observed in patients with CKD that were treated with low-phosphate diets. In contrast, diets with higher amounts of phosphate were associated with increases in the progression of CKD. In the REIN and REIN-2 cohorts, patients with higher serum phosphorus levels were associated with an incremental risk of progression or development of end-stage renal disease (ESRD). Interestingly, the investigators also found that elevated phosphate levels were associated with blunting of the renoprotective effects of the ACEi used [104]. A proposed mechanism for this blunting is that phosphate becomes a potent stimulus for fibroblast growth factor-23 (FGF-23) secretion. Stimulation of the FGF receptor common to all members of the FGF family increases the production of the ACE, which may activate the renin-angiotensin-aldosterone axis but undermines the effect of ACEI and contributes to the progression of CKD.

A high phosphate intake, especially in CKD patients who have high circulating levels of phosphates, promotes vascular calcification, a significant contributor to cardiovascular morbidity and mortality. Elevated phosphate levels induce vascular smooth muscle cells to undergo transformation into osteochondrogenic cells which produce bone matrix (apatite) just like osteocytes [105,106]. This pathologic adaptation can develop into deadly consequences by increasing coronary artery disease, stroke, and peripheral arterial disease. In patients with advanced CKD, medial arterial calcification can result in a necrotizing skin condition called calcific uremic arteriolopathy or calciphylaxis [107].

Dysregulation of proteolytic pathways in CKD

Proteins in all tissues are continually "turning over" (i.e., being degraded and replaced by new synthesis). The magnitude of the dynamic processes of protein synthesis and protein degradation is not small. Estimates of protein turnover indicate that normal adults degrade and resynthesize roughly 3%–5% of body proteins daily, and this occurs at measured rates of 3.5–4.5 g protein/kg/day [7,108–110]. This rate of protein metabolism is equivalent to breaking down and rebuilding 1–1.5 kg of muscle/day (based on the assumption that 20% of muscle weight is protein). From this perspective, processes of protein breakdown must be highly selective, otherwise, degraded protein would be irreversibly lost. Notably, the selectivity of protein degradation is not achieved by a mechanism based on a specific protease degrading specific proteins. Instead, different conditions or stimuli result in the activation of specific proteases that degrade proteins that have been identified for degradation.

In patients or models of CKD, there is an imbalance between protein synthesis and degradation, resulting in a net loss of protein stores. This loss of protein stores contributes to the morbidity and mortality that develops in CKD. For example, epidemiological and clinical reports document that muscle protein catabolism increases the risk of morbidity and mortality in CKD as it does in other catabolic conditions (e.g., heart failure, cancer, and aging) [111–113]. Specific contractile proteins lost from muscle account for about two-thirds of proteins in muscle and their loss is mainly responsible for the weakness and disability of patients who experience muscle wasting. Moreover, cross-sectional analyses indicate that muscle wasting is frequent and is detected in 40%–70% of patients with ESRD [114]. Besides the loss of body weight (principally, loss of muscle mass), there is a progressive reduction in the proteins that regulate metabolism and cellular renewal. Unfortunately, muscle protein wasting in patients with CKD is underappreciated and slowly progressive in many patients.

At least four major proteolytic pathways contribute to the loss of muscle protein in CKD. The pathways are lysosome-mediated protein degradation; intracellular proteolysis by calcium-activated proteases (calpains); ATP-dependent proteases (the UPS is the dominant process in this category); and poorly understood proteases that do not require energy for the losses of cellular proteins [7].

The ubiquitin–proteasome system

In all cells, including muscle, the UPS is the primary proteolytic system that degrades proteins. There is abundant evidence that CKD and its complications stimulate the UPS to breakdown proteins in muscle and other organs. Evidence for the primacy of the UPS is that enhanced protein degradation in isolated muscles of rodents with CKD is blocked by treatment with inhibitors of the proteasome [5,115]. There also is evidence that transcription of a similar set of genes when protein degradation arises in different models of muscle wasting (e.g., CKD, diabetes, starvation, and cancer) [116,117]. Since a large amount of proteins is being degraded each day and since these processes not only affect the regulation of cell processes but also affect the regulation of metabolic pathways, the specificity of the UPS must be exquisite. The selective degradation of different proteins is determined mainly by the cell's content of two E3 ubiquitin ligases, atrogin-1/MAFbx, and MuRF-1 [118]. The expression of these enzymes in muscle is correlated with the rate of muscle protein degradation.

The UPS initiates two multistep biochemical reactions: first, it "tags" proteins destined for degradation by conjugating them to ubiquitin (Ub), a member of the heat-shock protein family (Fig. 2.1). Secondly, the Ub-tagged protein is degraded by the 26S proteasome [119]. The process of Ub conjugation begins with the ATP-dependent activation of Ub by a single E1 isoform (Ub-activating enzyme). The activated Ub then interacts with one of 20–40 isoforms of the E2 Ub-carrier proteins, providing a degree of specificity to the identification of proteins to be degraded. An E2 Ub-carrier protein interacts with only a limited variety of substrate proteins. E3 ubiquitin ligases catalyze a more restrictive reaction. There are more than 1000 of these E3 Ub ligases, and each recognizes only a specific protein substrate (or class of proteins). Thus a specific E3 Ub ligase is activated only when it recognizes the protein to be degraded and transfers Ub to lysines in the substrate protein. The latter reaction is repeated until activated Ubs are transferred to form a chain of 4–5 Ub's that are attached to the target protein. This Ub chain can then be recognized by the 26S proteasome, a very large organelle consisting of >60 proteins that are organized into two particles, the 20S, barrel-shaped particle and 19S regulatory particles present at either or both ends of the 20S particle. Both particles have distinct activities. The 19S particle is capable of recognizing the polyubiquitin chain. In the presence of ATP, the 19S particle cleaves Ubs from the substrate protein so they can presumably be recycled. Also, the 19S particle unfolds the protein and translocates it into the 20S particle where it is degraded to peptides. The peptides are converted to amino acids by cytosolic peptidases. The importance of these reactions is underscored by the awarding of the 2004 Nobel Prize in Chemistry to Avram Hershko, Aaron Ciechanover, and Irwin Rose as discoverers of Ub and its biochemical role in protein degradation.

Both the conjugation of Ub to substrate proteins and the degradation of Ub-conjugated proteins are accelerated in muscle-wasting conditions. Considering the multiple steps required for the conjugation of Ub to a substrate protein and its degradation, it is not surprising that there is increased expression of key contributors to this process in muscle. These participants are recognized by increases in mRNAs of the components, including Ub, subunits of the 26S proteasomes, and two E3 Ub ligases, Atrogin-1 (also known as MAFbx) and MuRF-1. These E3 Ub ligases are critical for the breakdown of muscle proteins, and their expression increases dramatically (8- to 20-fold) in rodent models of muscle-wasting conditions [6,120–122]. In cultured muscle cells, the content of Atrogin-1 mRNA correlates closely with rates of protein breakdown, providing

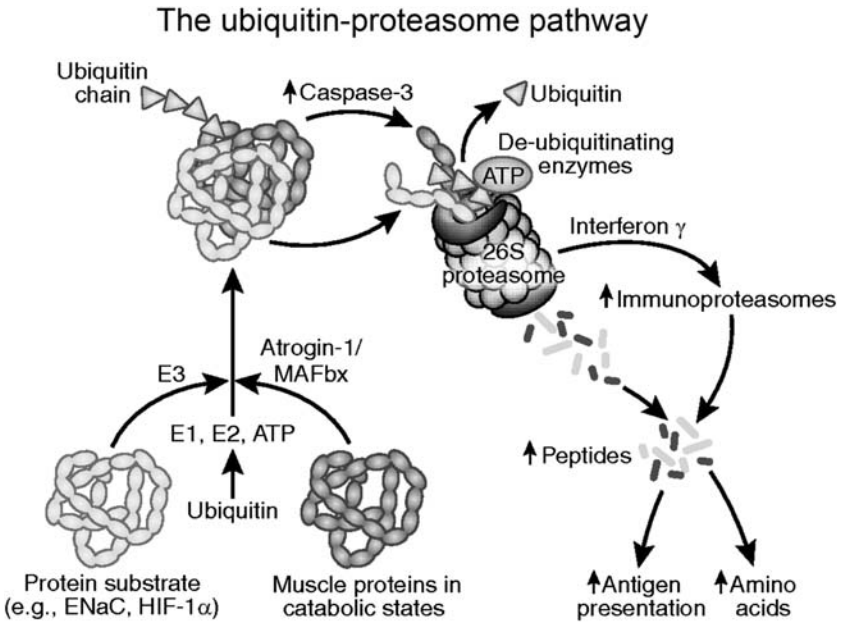

FIGURE 2.1 Various proteins including muscle are marked for proteasomal degradation by being linked to the polypeptide co-factor, ubiquitin. Caspase-3 cleaves muscle protein producing substrate for the Ub proteosome to subsequently degrade into small peptides. *ENac: Epithelial sodium channel, HIF-1: Hypoxia inducible factor-1 alpha.*

evidence of their importance. In patients, increased levels of mRNAs encoding Ub or subunits of the proteasome provide evidence for UPS activity in muscles of patients with trauma, cancer, CKD, or sepsis [123,124].

Understanding how Atrogin-1 and MuRF1 are activated is essential for understanding the regulation of protein metabolism. Two factors have been identified: the forkhead transcription factors (FoxO), and the inflammation-associated transcription factor (NFκB). To date, it is established that in conditions associated with impairment in insulin and IGF-1 signaling pathways such as CKD, diabetes, excess angiotensin II, and inflammation, there is enhanced activation of FoxO transcription factors. These responses result from decreased phosphorylation of FoxOs. Specifically, dephosphorylated FoxOs will translocate to the nucleus and increase the transcription of Atrogin-1 (and other genes). Alternatively, in response to inflammation, there is an activation of NFκB, which translocates to the nucleus to increase the transcription of the MuRF1, E3 Ub ligase, and mediators of inflammation [125,126].

In response to the progressive loss of kidney function, muscle protein synthesis decreases somewhat but the more prominent response is stimulation of protein degradation in muscle [127]. In addition to the critical role of the UPS, there is the participation of other proteases in causing muscle atrophy. The involvement of other proteases is necessary because the UPS readily degrades individual proteins in muscle, including actin, myosin, troponin, or tropomyosin, and it exhibits only limited proteolytic activity in degrading proteins present in complexes of proteins. This means that other proteases must initially cleave the muscle proteins that are present in complexes to produce substrates for the UPS [128]. In certain conditions including diabetes, excess angiotensin II, and inflammation plus CKD, we have found that the protease that performs this initial cleavage of proteins is caspase-3. These findings emphasize how CKD stimulates muscle proteolysis by activating a coordinated, multistep process. Specifically, a two-stage process is stimulated by specific signals (e.g., impaired insulin/IGF-1 signaling pathways, glucocorticoids, increasing degrees of inflammation) causing muscle wasting. First, there is an activation of the UPS and caspase-3. The latter performs an initial cleavage of the complex structure of actomyosin and myofibrils producing substrates for the UPS. Second, there is an increase in levels of mRNAs encoding specific components of the UPS. Using mRNA expression as an index of muscle wasting, it has been demonstrated that accelerated muscle wasting in CKD involves cellular mechanisms that are similar to those that cause muscle wasting in other catabolic conditions (e.g., cancer cachexia, starvation, insulin deficiency or resistance, and sepsis) [129]. These results indicate that there is a common transcriptional program that changes in a coordinated fashion to cause loss of muscle protein and, hence, muscle mass.

The role of caspase-3 was initially uncovered in cultured muscle cells when it was found that activated caspase-3 cleaves actomyosin, producing protein fragments that are rapidly degraded by the UPS. The role of caspase-3 extends beyond experimental rodent models of catabolic conditions. Specifically, the proteolytic action of caspase-3 leaves a “footprint,” a 14-kD C-terminal fragment of actin. The 14-kD actin fragment was most easily detected in the insoluble fraction of muscle; it was rarely present in the soluble fraction of muscle, presumably because the UPS rapidly degrades the 14-kD actin fragment. For example, the 14-kD actin fragment was found to be increased in skeletal muscle biopsies of patients with CKD or following burn injury or with severe osteoarthritis and muscle wasting. Regarding the influence of kidney disease, chronic hemodialysis patients were studied before and again after many weeks of exercise training. Compared to values in muscles of healthy adults, the 14-kD actin fragment was increased in muscles of hemodialysis patients but fell when the patients underwent exercise training [130].

Besides stimulation of metabolic pathways, we found that the participation of the increase in caspase-3 activity influences the activity of proteasome-mediated proteolysis in muscle. This response was linked to cleavage of specific subunits of the 19S particle of the proteasome suggesting that alteration of the specific subunits “opens” the entrance to the 20S proteasome, permitting substrate proteins to enter the proteasome where they are degraded [131]. These results, in addition to results from patients who had muscle atrophy following a burn injury, suggest that this actin fragment might potentially serve as a useful biomarker of accelerated muscle protein degradation. In summary, in rodent models and patients that respond to catabolic conditions, the activation of caspase-3 increases and this response stimulates increases in muscle protein degradation: firstly, caspase-3 performs an initial cleavage of complexes of muscle proteins, providing substrates for degradation by the UPS; and secondly, it stimulates the proteolytic activity of the proteasome. These properties exert a “feed-forward” stimulation of muscle proteins when caspase-3 is activated.

The calpains have also been suggested as a protease that an initially cleaves myofibrillar proteins to provide substrates for degradation by the UPS. Calpains are calcium-dependent, cysteine proteases that are activated in muscular dystrophy or sepsis-induced muscle wasting [132,133]. Their role in the digestion of muscle proteins in other conditions is unclear and the muscle wasting induced by CKD or conditions characterized by impaired insulin/IGF-1 signaling is not blocked by the inhibition of calpain activities.

Another contributor to CKD-induced muscle wasting is abnormal satellite cells. These cells are located underneath the basal lamina of myofibrils and function as muscle "stem" cells. Specifically, when muscles are injured or when muscle mass is low, satellite cells proliferate and then differentiate into myofibrils to increase the number and size of myofibrils [134]. Moreover, IGF-1 is a regulator of satellite cell responses and since we find that CKD impairs the proliferation and differentiation of satellite cells, these responses are notable because CKD impairs IGF-1 intracellular signaling [135].

Cytokine-induced muscle wasting

In addition to experimental information that increases in inflammatory cytokines stimulate muscle protein losses, there is evidence that dysfunctional mitochondria plus oxidative stress stimulate losses of muscle proteins [136–138]. Interestingly, certain inflammatory cytokines, particularly those stimulated by CKD and diabetes, exhibit reduced insulin sensitivity that appears to be a product of elevated circulating levels of tumor necrosis factor α (TNF-α) as a stimulus leading to insulin resistance and loss of muscle mass. Insulin-responsive cells including adipocytes and hepatocytes produce TNF-α, interleukin 6 (IL-6), and interleukin 1 (IL-1), and both tissue and circulating cytokine levels are increased by a high-fat diet [139]. In mice with insulin resistance, a high-fat diet actually increases the insulin resistance [140]. Hung et al. demonstrated that an IL-1 receptor antagonist can markedly suppress circulating levels of inflammatory cytokines in hemodialysis patients [141]. What is not known is whether these complications act synergistically to activate protein wasting in rodent models or patients with evidence of inflammation.

Myostatin

Myostatin is a member of the transforming growth factor-β (TGF-β family of secreted proteins), but unlike TGF-β, myostatin is predominantly expressed in skeletal muscle (low levels are also present in cardiac muscle and adipose tissues). In skeletal muscle, the myostatin precursor, prepromyostatin, is cleaved to promyostatin, which functions to produce an inactive, "latent complex." Myostatin is released from this complex and binds to a high-affinity, type-2 activin receptor (ActRIIB) present on muscle membranes [58]. Activation of this receptor leads to phosphorylation of SMAD transcription factors that regulate gene transcription. Notably, other TGF-β family members (e.g., activin A) can bind to ActRIIB and stimulate the same intracellular signaling pathway (Fig. 2.2). In skeletal muscle, the myostatin protein and its signaling pathway are increased in muscle-wasting conditions such as aging, responses to prolonged bed rest, AIDS, kidney failure, or heart failure [11,142–144]. Likewise, in models of cancer cachexia, glucocorticoid administration, mechanical unloading, and space flight, there are high levels of myostatin in muscle [145,146]. This is relevant because there is abundant genetic evidence that myostatin plays a pivotal role in regulating skeletal muscle mass and function. For example, deletion of the myostatin gene in mice causes a dramatic increase in the sizes and number of skeletal muscle fibers. Besides mouse phenotypes, cattle, sheep, dogs, and a human bearing a loss-of-function myostatin mutation will exhibit an enormous increase in muscle mass [147–149]. These myostatin mutations can influence athletic performance: whippet dogs bearing a single copy of the myostatin mutation are among the fastest dogs in racing. However, whippets bearing two copies of the same mutation have such a large amount of muscle mass that they win no races. Likewise, myostatin polymorphism in elite thoroughbred horses suggests these horses have a decided advantage regarding swiftness [150]. Since myostatin deficiency does produce muscle hypertrophy and can improve physical performance, manipulating myostatin might block muscle wasting, and this could be the basis for a therapeutic strategy.

Myostatin inhibition in CKD mice was found to be associated with decreased circulating levels of inflammatory cytokines and especially, IL-6. In fact, earlier results demonstrated that an increase in IL-6 and the acute phase protein, serum amyloid A acted synergistically to impair intracellular IGF-1 signaling [151]. The resulting decrease in p-Akt in muscles led to acceleration of protein degradation in muscles. Muscle treatment with the antimyostatin peptibody corrected these responses and blocked the CKD-induced muscle catabolism. Finally, it was shown that treatment of cultured muscle cells with TNF-α actually raised myostatin production in muscle cells. However, treatment of muscle cells with myostatin increased the production of IL-6. To date, treatment of CKD patients with the antimyostatin peptibody has not successfully blocked the losses of muscle mass.

Albumin and other markers of malnutrition

There is a familiar relationship between low values of serum albumin and increased mortality in CKD and

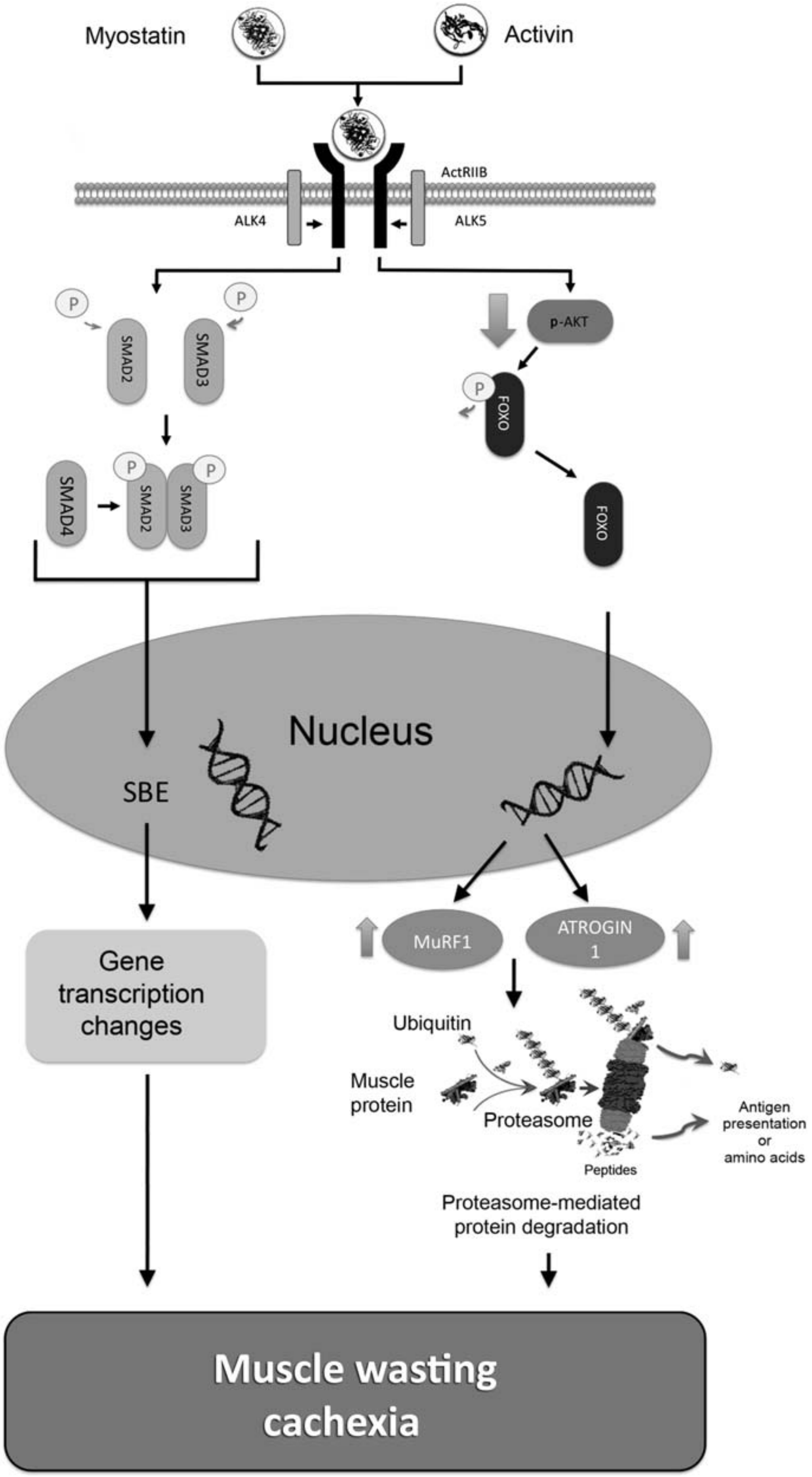
Myostatin
Activin
ActRIIB
ALK4
ALK5
P
SMAD2
SMAD3
p-AKT
FOXO
SMAD4
Nucleus
SBE
MuRF1
ATROGIN 1
Gene transcription changes
Ubiquitin
Muscle protein
Proteasome
Peptides
Antigen presentation or amino acids
Proteasome-mediated protein degradation
Muscle wasting cachexia

FIGURE 2.2 Myostatin and Activin bind to ActRIIB receptor and stimulate muscle degradation by activation of SMAD transcription factors that promote muscle degradiation. The ActRIIB receptor also stimulates the Ub-proteosome pathway. *SBE: SMAD binding element.*

dialysis patients. Initially, this relationship was generally attributed to eating an inadequate diet (i.e., malnutrition-induced loss of muscle mass) [152]. This perception is erroneous for the following reasons. First, if protein malnutrition was the cause of defects in protein stores, then low values of serum albumin should be corrected by merely altering the diet. Unfortunately, changing the diet rarely reverses the loss of protein stores in patients with CKD. Serum albumin should be used primarily as a predictor of hospitalization and mortality rather than a sensitive index of nutritional status or adequacy of dietary protein.

It is useful to track changes in body mass index (BMI) and serum potassium and phosphorus levels in patients with advanced CKD and ESRD patients because low values can indicate an increased risk of malnutrition. Alternatively, decreasing values of BMI may be influenced by changes in total body water related to increased salt intake. In CKD patients with limited residual renal function, the expected interdialytic weight gain, as a percentage of body weight, is between 2% and 5%; <2% fluid gain can indicate inadequate fluid or food intake and may predict a decrease in body mass [153]. It is critically important to screen patients for the possibility of underdialysis (using urea kinetic modeling: Kt/V) resulting in accentuated uremic symptoms such as nausea, taste changes, acute or chronic gastrointestinal dysfunction, fatigue, and depression. Kinetic modeling can be used to estimate protein consumption, by measuring the normalized protein nitrogen appearance (nPNA), and nitrogen balance is best achieved by consuming 1.2 g/kg of protein daily in this group of patients (see Chapter 31: Nutritional Management of Maintenance Hemodialysis Patients, and Chapter 32: Nutritional Management of Chronic Peritoneal Dialysis Patients) [154,155]. It is also vital to assess the socioeconomic status and address food insecurity with assistance programs, if needed.

Defining decreased protein stores

Reduced protein stores in patients with CKD will contribute to increases in their morbidity and mortality but it is difficult to assign a cause–effect relationship with malnutrition. A significant dilemma in establishing a cause–effect relationship is the lack of consensus surrounding definitions of muscle wasting. In 2008 the International Society of Renal Nutrition and Metabolism proposed that low values of serum albumin, prealbumin, and cholesterol plus abnormalities in body weight and anthropometry could identify patients with CKD who have lost protein stores [156]. They also suggested a new descriptive term, protein-energy wasting or PEW, as a method of classifying affecting patients. Other diagnoses used to detect reduced protein stores in CKD patients were abandoned because they were imprecise. For example, sarcopenia was discarded because it generally describes the loss of muscle mass associated with aging. Cachexia was discarded because it implies a more severe state of protein depletion. An alternative Consensus Conference concluded that the loss of muscle mass without loss of adiposity be labeled as cachexia [157]. Others have recommended that a cachexia diagnosis should include a 5% loss of edema-free body weight within 12 months plus anthropometric evidence of muscle wasting, and the evidence of inflammation and hypoalbuminemia. We have not identified a more accurate diagnosis of lost muscle mass. But, there is interest in using the new tools based on loss of muscle mass identified by CT scanning or magnetic resonance imaging (MRI) but the cost for follow-up evaluations could be prohibitive [158].

Although less expensive, estimates of lean body mass from bioelectric impedance and dual-energy X-ray absorptiometry are of limited value because they do not readily distinguish between fluid and tissues, and the lean body compartment is derived [159]. Finally, these problems can be avoided by measuring body composition by the presence of potassium and nitrogen isotopes using whole-body counters [160]. This measurement is noninvasive and accurate, but the technique is only available at a handful of sites in the world. Recently, a noninvasive method to estimate muscle mass based on creatine (D3-creatine) dilution using fasting morning urine has been developed. In one report, D3-creatinine urinary enrichment from the day provided muscle mass estimates that were correlated with MRI ($r = 0.88$, $P < .0001$) [161]. The technique relies on a consistent fraction of the ingested label to be incorporated in the total creatinine pool and has intrasubject variability as a result of urine collection methods. Furthermore, the reliability of these measurements is unknown in patients with labile SCr and advanced CKD, but the test may be useful in appropriate clinical and research settings.

Protein supplementation in dialysis

Protein-energy wasting estimated from circulating albumin affects up to 60% of hemodialysis patients and is a strong predictor of mortality. Hemodialysis is associated with the loss of 10–12 g of amino acids, and in peritoneal dialysis patients, 5–15 g of albumin is lost daily depending on the number of exchanges [162,163]. The catabolism related to the dialysis is not limited to the time patients are exposed to the procedure; Ikizler et al. measured protein synthesis and degradation in fasting hemodialysis patients using standard techniques of labeled amino acid turnover and found the catabolic state endured after dialysis treatment [164]. Specifically, they measured the components of protein metabolism before, during, and at 2 hours after completing the dialysis treatment. At all three points, protein degradation exceeded protein synthesis suggesting that the dialysis procedure can activate metabolic pathways that stimulate the loss of body protein stores.

Clinical practice guidelines for dialysis patients recommend nutritional counseling and adding oral nutrition supplements as first-line treatment. If this proves ineffective, then enteral tube feeding is recommended. When oral or enteral feedings are not feasible, then parenteral nutrition is an option. The effect of protein supplementation using intradialytic parenteral nutrition during dialysis (IDPN) has been investigated, and protein balance is improved [165]. Specifically, when IDPN is given during dialysis, it improved both the rates of protein synthesis and degradation, but it did not prevent the persistent increase in protein degradation after dialysis. In another evaluation, the investigators compared the responses associated with the administration of IDPN to those induced by an oral nutritional supplement given during hemodialysis. Protein balance improved with both IDPN and the oral supplement, but whole-body protein balance was still negative [166]. These careful studies indicate that dialysis must activate or stimulate catabolic pathways in CKD patients, increasing the risk of muscle protein wasting. The results indicate that the unidentified, catabolic pathways are not “turned off” by increasing dietary constituents. An early report by Capeli et al. examining clinical outcomes in patients treated with IDPN showed correction of hypoalbuminemia and improved mortality, and a more recent study showed significant improvement in prealbumin levels [167,168]. However, other investigators have not found that IDPN decreases hospitalizations or improves mortality [169,170]. After two years, the supplement had improved the serum concentration of albumin. Unfortunately, the supplement did not improve mortality, BMI, laboratory markers of nutritional status, or the rate of hospitalization. Taken together, these reports suggest that correcting metabolic abnormalities induced by ESRD or at least blunting their physiologic influence should be further investigated.

Protein metabolism post-kidney transplantation

There have not been many investigations of mechanisms affecting protein metabolism in patients following kidney transplantation. Available results indicate that post-kidney transplant, patients gain significant increases in weight just after successful kidney transplantation and in subsequent years. Could the post-kidney transplant gain in weight arise from improvements in protein status, to the accumulation of salt and water or to accumulation of fat mass, or to a combination of these factors? It has been speculated that the post-transplant weight gain could be due to the accumulation of muscle mass but increased size of this organ was not uncovered in a recent report [171,172]. In other analyses, it has been concluded that muscle mass did not increase in kidney transplant recipients [173].

It is well established that insulin resistance is a serious complication of patients with either CKD or kidney transplantation, extending even to the development of post-transplant diabetes [174]. The increase in the body weight of kidney transplant patients is primarily related to increased fat mass. Whether this altered body composition is due to glucocorticoid-induced altered fuel metabolism is unclear. However, the development of insulin resistance would suppress muscle mass and account for the observation that muscle mass did not increase despite a gain in both body weight and physical activity [175]. On the other hand, analyses of body composition indicate that there is a demonstrable association between the accumulation of visceral adipose tissue and the development of insulin resistance.

Factors that may contribute to the development of weight gain and insulin resistance include corticosteroid treatment, but this is not the only cause since insulin resistance can develop in kidney transplant patients that are treated with steroid-sparing protocols. For example, corticosteroid withdrawal from kidney transplant patients after only 7 days revealed that both placebo-treated and corticosteroid-treated patients gained a significant amount of weight [176,177]. Thus in patients receiving only low amounts of corticosteroids, this hormone is unlikely to be a primary factor accounting for weight gain. Other factors associated with the increase in weight include African American race, young age, female gender, modality of dialysis, use of tacrolimus-based immunosuppression, and poorly defined genetic factors [178–180].

Conclusion

There is over a century-old observation that loss of kidney function leads to altered protein metabolism, which affects the course of kidney disease by producing uremic toxins, stimulating inflammation, and a deterioration of homeostatic functions of the kidney. Despite efforts directed at identifying physiologic and molecular mechanisms that change protein metabolism, there remain unanswered questions: (1) how are specific uremic toxins generated, and how can the toxicity of potential toxins be tested and prevented? (2) What are the mechanisms that result in loss of muscle mass and, ultimately, increasing frailty, morbidity, and mortality? (3) In CKD, what is the mechanism that raises circulating inflammatory cytokines, increases glucocorticoid production, and impairs insulin/IGF-1 signaling leading to proteolysis if body protein stores? Not surprisingly, multiple techniques have been investigated to determine if they can successfully block muscle protein losses and the loss of kidney function. A potentially successful strategy has been to limit the amount of protein and acid-generating compounds in the diets of patients with CKD. This can be accomplished either by providing alkali therapy or by modifying diet to include increased amounts of fruit and vegetables in meals and by prescribing low-protein diets or very low-protein diets that provide 0.3 g protein/kg/day plus ketoacids to patients with CKD. Notably, the success of changing the diet requires regular evaluations of compliance with dietary interventions; this is possible when compliance is based on analyses of urea kinetics. In designing diets of patients with CKD, there are other factors to consider besides protein and calorie adequacies, namely, diets rich in protein also are rich in phosphates and salt. This is relevant because inattention to their role in the design of diets can interfere with the function of drugs such as inhibitors of the renin–angiotensin–aldosterone that can slow the progression of CKD. As long as there is kidney disease, there will be a need for a trained focus on nutrition, and as new therapeutics enter the market for CKD, it would be wise to assess their influence on protein metabolism.

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CHAPTER

3

Carbohydrate metabolism in chronic renal disease

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Introduction

In patients with chronic kidney disease (CKD), disorders of carbohydrate metabolism are encountered at different levels of the insulin-glucose cascade. The two major abnormalities that underlie glucose intolerance in CKD are resistance to the peripheral action of insulin and impaired insulin secretion. When these two metabolic disturbances are present glucose intolerance ensues [1]. Patients with CKD stage 5 are frequently resistant to the peripheral action of insulin. Consequently, plasma insulin concentrations tend to be higher at any given rate of insulin secretion [2,3] (Table 3.1).

Insulin resistance

Insulin resistance is a state of impaired biological response to normal circulating levels of insulin that is accompanied by hyperinsulinemia to maintain normal plasma glucose concentration. Patients with insulin resistance experience lipid accumulation and increase in lipolytic activity in adipose tissue .

As first reported in detail by Westervelt and Schreiner, using the forearm perfusion technique, peripheral glucose uptake is reduced in CKD [5]. This observation was confirmed by DeFronzo and Alvertrand [6] using the gold standard method, the euglycemic insulin clamp technique, which allows to quantitate the amount of glucose metabolized per unit of insulin. Such peripheral resistance to insulin is seen even in the early stages of CKD. In a study of glucose and insulin in renal disease (SUGAR) [7], it was shown that in nondiabetic patients with moderate to severe CKD, glucose intolerance and hyperinsulinemia are common. In this study, insulin sensitivity measured by the euglycemic insulin clamp technique was unrelated to the eGFR. Overall, demographic factors, physical activity, diet, smoking, adiposity, and lean body mass explained decrease of insulin sensitivity in CKD [7]. What is the prevalence of insulin resistance in CKD patients? In the ULSAM study based on the euglycemic insulin clamp technique, the prevalence of insulin resistance in Caucasian elderly men with an eGFR <60 mL/min, was 24% [8]. In the study performed in hemodialysis (HD) patients, the prevalence of insulin resistance measured by the homeostatic model (HOMA-IR) was 32% [9].

Both liver and kidney are the major sites of glucose production in the fasting state [10,11]. Liver and skeletal muscles are the major sites of peripheral glucose uptake. The available data indicate that glucose production by the liver is not altered in CKD. Specifically, DeFronzo and coworkers documented that baseline hepatic glucose production and its suppression by insulin were not altered in patients with CKD [3,6]. In addition, glucose uptake by the liver seems to be not affected in CKD [6]. The renal contribution to glucose production has long been grossly underestimated and is in fact quite substantial [12].

The main site of decreased insulin sensitivity is skeletal muscle. The defect is not at the level of the insulin receptor: in skeletal muscles of rats with chronic uremia the numbers and affinities of the receptors are normal [13], as well as, insulin receptor kinase activity [14]. The defect is presumably at the postreceptor level [15].

There is also information on insulin postreceptor defect in CKD and uremia. When the β chain of the receptor has been phosphorylated, a complex series of interactions follows involving insulin receptor substrate

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TABLE 3.1 Abnormalities of carbohydrate metabolism in chronic kidney disease.

- Usually normal fasting blood glucose, but tendency to spontaneous hypoglycemia
- Fasting hyperinsulinemia with prolonged insulin half-life
- Elevated plasma glucagon and growth hormone concentrations
- Impaired glucose tolerance

(IRS) as well as numerous cofactors [16,17]. More distal effects (e.g., stimulation of proliferation) are mediated via the mitogen-activated protein kinase pathway and the inositol-triphosphate (IP3) pathways.

The latter is responsible for the upregulation of the insulin-regulated glucose transporter (GLUT-4). The PI3-K complex is a heterodimer composed of an 85-kDa (p85) regulatory subunit and a 110-kDa (p110) catalytic subunit. The subunits and the p85−p110 complexes are differentially regulated by glucocorticoids [18,19]. Stimulation of p85 expression by glucocorticoid treatment leads to the reduction of PI3-K activity [19]. This may be relevant because glucocorticoid synthesis is increased in uremia [20].

In uremia the insulin-dependent glucose uptake is altered. GLUT-4 is unique to muscle and adipose tissue. The expression of GLUT-4 in muscle cells of subtotally nephrectomized rats is reduced [21]. Carbamylation of proteins is a common finding and modifies signal transduction and translocation of GLUT-4. It has been shown that *N*-carbamoyl-L-asparagine reduces insulin-sensitive glucose uptake by interfering with GLUT-4 activity [22].

As mentioned earlier, insulin-resistant frequently occurs even at the early stages of renal disease and becomes even highly prevalent in patients with advanced CKD, however. The resistance to the peripheral action of insulin markedly improves after several weeks of HD and of peritoneal dialysis (PD) [23,24]. Presumably, an unidentified dialyzable uremic "toxin," possibly a protein breakdown product, is involved in the genesis of impaired insulin action. Sera of uremic patients contain a compound that inhibits glucose metabolism by normal rat adipocytes [25]. This compound with a molecular weight of 1−2 kDa is specific for uremia, because it is not found in nonuremic patients with insulin resistance. Hippurate accumulates in the blood of patients with CKD and inhibits glucose utilization by rat diaphragm, brain, kidney cortex, and erythrocytes. It may therefore contribute to insulin resistance of patients with CKD [26]. It was also found that p-cresyl sulfate promotes insulin resistance associated with CKD [27].

A number of further factors have been identified which are involved in the genesis of insulin resistance in kidney disease and some of them are potential targets for intervention.

Increased visceral fat is an important risk factor for insulin resistance both in the general population and in CKD [28]. Insulin resistance by HOMA-IR is closely linked to both fat mass and body mass index (BMI) in CKD [28]. Ramos et al. [29] documented that even in nonobese, nondiabetic patients with advanced CKD, BMI and adiposity were associated with increased F2-isoprostanes and C-reactive protein plasma concentrations and negatively correlated with protein thiol's plasma concentrations. They concluded that adiposity amplifies oxidative stress and inflammation [29].

It has been postulated that resistin, a hormone derived from adipose tissue, is involved in the genesis of insulin resistance [30]. Plasma resistin concentrations are high in CKD patients, probably the result of diminished renal clearance [31]. In CKD, however, no relation was found between insulin sensitivity and plasma resistin concentrations [31].

A sedentary lifestyle causes insulin resistance [32]; conversely, exercise training improves insulin sensitivity. It was shown both in experimental [33] and clinical studies [34,35] that this applies for CKD as well.

Plasma concentrations of the insulin antagonists glucagon [36,37] and growth hormone [38,39] are frequently elevated in CKD. It has been proposed that these two hormones contribute to insulin resistance. However dialysis improves insulin sensitivity without changing the concentrations of growth hormone and glucagon [40,41].

Metabolic acidosis is frequent in CKD [42]. Observational studies in CKD patients with the euglycemic insulin-glucose clamp technique showed that metabolic acidosis is associated with insulin resistance [22,43,44]. Results of experimental studies suggest that metabolic acidosis leads to insulin-induced internalization defects and accelerates the dissociation of insulin from its receptor [45,46]. A causal role in insulin resistance is suggested by the observation that correction of acidosis by bicarbonate improves insulin resistance in CKD patients [44,47].

A finding with a major clinical relevance is the observation that in uremia major insulin resistance is caused by inflammation. The molecular pathways following insulin binding to its receptor includes tyrosine phosphorylation of members of IRS family. This process triggers translocation of GLUT-4 from intracellular stores to the cell membrane [48]. Conversely, serine phosphorylation of IRS-1 abrogates the association between IRS-1 and insulin receptor leading to a state of insulin resistance [49]. Inflammatory mediators such as tumor necrosis factor α (TNF-α) may activate serine kinases such as c-jun-NH2 e terminal-kinase (JNK) and IkB kinase (IKK) which phosphorylate serine residues of IRS-1 and disrupt insulin signaling [50].

Insulin resistance is involved in the development of a catabolic state during uremia. Muscle catabolism in inflammatory states is mediated by proinflammatory cytokines, for example, interleukins 1 and 6 (IL-1 and IL-6) and TNF-α [51–53]. These cytokines act also on the satiety center [54,55]; this may explain the tight relationship between anorexia and the plasma concentration of the proinflammatory cytokines in HD patients [56,57].

Another observation is the potential role of anemia which by decreasing tissue oxygenation may lead to insulin resistance [58] which is ameliorated by erythropoietin treatment [59–61].

Low plasma concentration of 1,25-dihydroxycholecalciferol (1,25$(OH)_2D_3$) is common in CKD patients, especially at CKD stage 4 or 5 [62]. It was shown that, in CKD 3 and 4 patients, therapy with an active form of vitamin D or with cholecalciferol did not affect insulin resistance [63]. These results suggest that vitamin D has no role in the pathogenesis of insulin resistance in CKD. In contrast, metaanalysis of 17 clinical trials completed in HD patients showed that vitamin D therapy (mainly as an active form) improves insulin sensitivity [64]. The mechanisms by which vitamin D improves insulin sensitivity in HD patients remain unknown.

Finally, it is known that angiotensin II (Ang II) [65,66] interferes with insulin sensitivity in individuals without kidney disease. Ang II contributes to insulin resistance in CKD as suggested by the observations of Satirapoj et al. in HD patients. Indeed, valsartan reduced fasting insulinemia and insulin resistance as assessed by the homeostatic model (HOMA-IR index) [67]. Moreover, Cioni et al. showed in PD patients that telmisartan improves insulin sensitivity also measured by HOMA-IR indexes [68].

Consequences of insulin resistance

Insulin resistance seems to be a clinically important parameter, because in insulin resistant patients CKD progression, may be accelerated [69,70]. In CKD patients, insulin resistance is closely associated with increased cardiovascular risk [8,71]. Shinohara et al. [71] followed 183 nondiabetic HD patients for more than 5 years. CV deaths by Kaplan–Meier estimation were significantly more frequent in subjects in the top tertile of insulin resistance, assessed by the HOMA-IR index, compared to the lower tertiles. The adverse effect of insulin resistance on mortality was independent of body mass, hypertension, and dyslipidemia. In CKD patients, insulin resistance is closely associated with cardiovascular risk factors, including oxidative stress [72], chronic inflammation [72], and endothelial dysfunction [73]. Moreover, insulin resistance may contribute to hypertension [74]. It was shown that insulin resistance increases salt sensitivity via an increased tubular sodium reabsorption [75]. Insulin resistance might also lead to lipid abnormalities. Insulin is an important regulator of lipoprotein lipase activity (LPA). Insulin resistance is associated with reduced LPA activity [76]. Lipoprotein lipase plays a major role in triglyceride removal. In CKD patients, LPA activity is reduced and presents the major cause of hypertriglyceridemia [77]. Further support for the role of insulin in the genesis of dyslipidemia is provided by the observation that administration of insulin to uremic rats corrects the defect in LPA as well as hypertriglyceridemia [78]. Insulin resistance may also participate in the pathogenesis of malnutrition commonly found in CKD patients [48,79]. In rats with acute kidney injury, protein degradation is increased in perfused or incubated muscle. This defect is closely related to abnormalities in insulin-dependent carbohydrate metabolism [80]. Insulin deficiency (or resistance) stimulates breakdown of muscle proteins and activates a common proteolytic pathway via the ubiquitin-proteasome system [81,82]. Therefore insulin resistance may also contribute to increased protein catabolism and malnutrition in CKD patients.

Insulin secretion

Insulin secretion by the β cells of the pancreatic islets is a complex process. The β cells are stimulated both by nutrients (glucose, amino acids, and fatty acids) and nonnutrient agents, for example, hormones and neurotransmitters. The islets use different mechanisms to detect nutrient and nonnutrient stimuli, but insulin secretion uses the same intracellular processes irrespective of whether the β cells are activated by nutrient or nonnutrient secretagogues [27].

Glucose-induced insulin secretion involves glucose uptake by the β cells, followed by glucose metabolism and production of adenosine triphosphate (ATP). ATP facilitates the closure of ATP-dependent K channels, followed by cell membrane depolarization and subsequent activation of voltage-sensitive Ca channels. As a consequence, calcium enters the islets causing an acute rise in cytosolic Ca concentration, thus triggering the secretion of insulin (through exocytosis of insulin–containing granules) [83].

A number of studies showed that insulin secretion is impaired in CKD [84–87]. One factor responsible for impaired insulin secretion in CKD is high plasma parathormone (PTH) concentration. Insulin secretion, as assessed by the hyperglycemic clamp technique, is improved when the parathyroid gland is suppressed [88,89]. Using the technique of isolated pancreatic islets the underlying molecular mechanisms have been elegantly demonstrated in subtotally nephrectomized (SNX) rats by Fadda et al. [84]; insulin release triggered by glucose (but not by the alternative agent glyceraldehyde) was diminished in SNX rats and this outcome was almost completely prevented by parathyroidectomy [84,90]. The mechanism underlying PTH-induced impairment of insulin secretion is an increase in cytoplasmic Ca concentration in pancreatic beta cells as a result of increased Ca entry, followed by decreased Ca extrusion and the resulting reduction of ATP content. As a result, closure of ATP-dependent K channels occurs with consecutive reduction of the glucose-induced Ca signal. Glucose-induced insulin secretion is impaired even in rats with normal renal function when they receive daily injections of PTH [90,91].

Apart from glucose, amino acids are stimuli triggering insulin secretion, the most potent being L-leucine [92], and an additional stimulus is K [93]. In CKD, such insulin secretion triggered by the alternative stimuli L-leucine [87] or K [85] is also impaired.

Similarly to animal experiments, in uremic patients, reduced insulin secretion in response to secretagogues is mainly the result of chronic PTH excess. This was documented by Mak and coworkers in children treated by hemodialysis, whose insulin secretion increased after parathyroidectomy [88,89].

1,25$[OH]_2D_3$ affects insulin secretion as well. Islet cells express both vitamin D receptors [94,95] and vitamin D–dependent calcium-binding protein [96]. After administration of labeled 1,25$(OH)_2D_3$, radioactivity is retrieved in the cells [97]. Insulin secretion is impaired in vitamin D–deficient rats with normal renal function [98]; the defect is reversed by vitamin D [99]. This may be relevant for CKD, because acute intravenous administration of 1,25$(OH)_2D_3$ to dialysis patients improved the early and late phases of insulin secretion [100].

Insulin clearance

The kidney plays an important role in insulin metabolism and clearance. Insulin is filtered by the glomeruli and reabsorbed in the proximal tubule [101]. In normal subjects the renal clearance of insulin is about 200 mL/min [102]. This value exceeds the glomerular filtration rate (GFR), indicating that in addition, peritubular uptake of insulin takes place [103]. It is estimated that 6–8 U of endogenous insulin are removed daily by the kidney, accounting for 25%–40% of the total removal of endogenous insulin. A decrease in the metabolic clearance rate of insulin is demonstrable in patients with GFR <40 mL/min; a significant prolongation of the insulin half-life is observed when GFR falls below 20 mL/min [104]. The endogenous insulin clearance increases remarkably when dialysis treatment is started; presumably, this is explained by an increase in insulin removal by liver and muscle.

In CKD patients, diminished renal [104] and extrarenal (liver and muscles) [105] insulin clearance accounts for fasting hyperinsulinemia. It also accounts for decreased insulin requirements in diabetic patients with impaired kidney function.

Hypoglycemia

Hypoglycemia may lead to serious complications. Severe hypoglycemia may results in acute mental status changes such as: seizures and coma [106]. Clinical studies suggest that patients with hypoglycemia are more prone to cardiac arrhythmias [107] or to stroke [108].

Clinical observation showed that CKD patients, both diabetic and nondiabetic, are particularly at hypoglycemia risk [109–112]. In a retrospective cohort analysis comprising 243,222 Veterans Health Administration patients, hypoglycemic episodes (<70 mg/dL) were more frequent in diabetic as well as nondiabetic patients with CKD compared to no CKD; the risk of death within 1 day after hypoglycemia <70 mg/dL was markedly elevated [112].

The mechanism underlying spontaneous hypoglycemia in CKD patients is not completely elucidated. It is important to be aware of the fact that in contrast to the previous opinions gluconeogenesis is not restricted to the liver. Recent studies document that the kidney contributes to no less than 40% of overall gluconeogenesis [12]. In type 2 diabetic patients, the overall glucose production is increased by as much as 300%; hepatic and renal gluconeogenesis contribute equally to this increase [113]. Moreover, a reduction in hepatic glucose production was found, due to diminished availability of substrate for gluconeogenesis [109]. Malnutrition, impaired glycogenolysis, and impaired degradation of insulin may all contribute to spontaneous hypoglycemia [106,114]. Nondiabetic HD patients treated with glucose-free dialysate frequently develop hypoglycemia [114]. However nowadays most dialysate solutions content to 200 mg/dL glucose to avoid these events. In diabetic patients with CKD, decreased degradation of the administered insulin may result in higher than expected blood insulin levels. This may potentially precipitate hypoglycemia. Repeated episodes of hypoglycemia are occasionally the first clinical sign drawing attention to the presence impaired renal function. Careful adjustment of the insulin dose is then needed. Some researchers reported that insulin dose could be reduced by 40%–50% [106]. When diabetic patients with impaired renal function are treated with antidiabetic agents, it is important to consider that some of these agents or their active metabolites are cleared via the kidney and cumulate in CKD patients [106]. Therefore some of these drugs become contraindicated, and appropriate dose adjustment is necessary for the others (see below).

Carbohydrate metabolism in patients with renal replacement therapy

Patients undergoing maintenance hemodialysis

The initiation of renal replacement therapy by HD reduces insulin resistance. This was first reported by Kobayashi et al. [22] in a study using the hyperinsulinemic—euglycemic clamp technique. It has also been shown that the use of high-flux membranes lowers insulin resistance in HD patients compared to treatment with low-flux membranes [115,116]. It is relevant that many uremic patients with diabetes have so-called burnt-out diabetes [117], i.e., their, hyperglycemia disappeared after weight loss resulting from anorexia. On the other hand, in patients with terminal uremia and no known history of type 2 diabetes, but with a pathological oral glucose tolerance test, diabetes may reappear after refeeding following the start of HD treatment. This was seen in 10% of type 2 diabetic patients entering the HD program.

In nondiabetic and particularly diabetic HD patients the blood concentrations of glucose and insulin may be affected by the dialysis procedure and particularly by the dialysate glucose concentration. Blood glucose is lost into the dialysate downhill, a concentration gradient, if the dialysate is glucose free; therefore glucose-free dialysate is currently no longer used. Today, the usual dialysate glucose concentrations range between 100 and 200 mg/dL; the net effect will be lowering of markedly elevated glucose levels and protection against hypoglycemia during dialysis sessions [118]. Plasma insulin levels may also decrease during HD sessions as a result of potential glucose load (depending on dialysate glucose concentration) and of insulin clearance (the rate of loss varying between membranes).

Additional metabolic effects of dialysis include improved insulin sensitivity and potential decrease of counter-regulatory hormones (e.g., growth hormone), etc. In dialyzed diabetic patients, signs and symptoms of hyperglycemia may be modified: in addition to the classical signs, that is, thirst, fluid overload, and severe hyperkalemia, the absence of polyuria precludes volume contraction and may even cause volume expansion or pulmonary edema, particularly in the presence of excessive thirst. Further potential complications of hyperglycemia include increased blood pressure, altered mental status, nausea, and gastroparesis, but symptoms and signs are frequently nonspecific or lacking.

Antidiabetic therapies require special consideration in diabetic HD patients (see also below). The insulin dose must be reduced, often by as much as half. Rapid-acting insulin analogs are less likely to cause hypoglycemia than regular or long-acting insulin, because their pharmacokinetics are less affected by renal failure [119]. Most oral antidiabetic drugs are contraindicated in CKD stage 5 patients, and on dialysis, thiazolidinediones (TZDs), meglitinides, and dipeptidyl-peptidase 4 (DPP-4) inhibitors are the drugs that can be used in HD patients [106,120].

Peritoneal dialysis patients

The initiation of renal replacement therapy by PD reduces insulin resistance as shown by Kobayashi et al. [22]. By contrast, some patients develop new-onset hyperglycemia after the start of PD, presumably as a result of high peritoneal glucose load [121,122]. PD patients tend to have higher fasting glucose, blood HbA1c, and HOMA-IR indices compared to hemodialyzed patients, possibly as the result of high glucose load and weight gain [123,124]. Depending on the dwell time and the exposure to high glucose PD solution, up to 80% or more of glucose in the PD solution is absorbed, accounting for a daily glucose load of up to 100—300 g of glucose [125,126]. The absorption of glucose from the dialysis solution predisposes to hyperinsulinemia, weight gain, and insulin resistance. Icodextrin, an osmotically active glucose polymer, can be used as an osmotic agent to substitute for glucose. Clinical studies indicate that reduction of hyperinsulinemia and increased insulin sensitivity can be achieved by long-term use of icodextrin-containing PD solutions for overnight exchanges [127,128].

Kidney transplant recipients and new-onset diabetes after transplantation

The first description of diabetes mellitus as a complication of kidney transplantation dates back to 1964 [129]. Baseline risks that predispose kidney graft recipients to new-onset diabetes after transplantation (NODAT) include advanced age, obesity, male gender, hepatitis C virus infection, nonwhite ethnicity, and family history of diabetes, which are inherited, as well as, acquired defects in insulin sensitivity and β cell function [130,131]. The high incidence of NODAT in predisposed individuals during the first months after transplantation reflects superimposition of new transplant-specific factors upon a predisposing baseline metabolic milieu. The best documented transplantation-specific factors include immunosuppressive agents, for example, glucocorticoids, calcineurin inhibitors (cyclosporine and particularly tacrolimus), sirolimus, and weight gain after transplantation [130,131] (Table 3.2).

NODAT will become even more frequent in the future given the current pandemic of obesity. Based on ADA (American Diabetes Association) criteria of diabetes mellitus, Cosio et al. [132] reported that 1 year after transplantation, the prevalence of NODAT was 13%. In one of the largest epidemiologic studies of NODAT, Kasiske et al. found, in 11,659 Medicare beneficiaries with a first kidney transplant, a cumulative incidence of NODAT of 9%, 16%, and 24% at 3, 12, and 36 months, respectively [133]. Many clinical studies in recipients of kidney and other solid organ transplants showed that NODAT is associated with an increased risk of graft failure as well as death when compared with graft recipients without NODAT [134]. The excess mortality is mainly attributable to a higher incidence of CV disease. The therapy of NODAT includes both nonpharmacological and pharmacological interventions: aggressive lifestyle modification, particularly dietary changes, exercise, and weight loss irrespective of whether the patient requires pharmacologic treatment for hyperglycemia or not [130,131,135]. The choice of antidiabetic agents depends mainly on transplanted kidney function. No antidiabetic drug is specifically contraindicated in patients after kidney transplantation, and pharmacological interventions are similar to those used in general diabetic population. The role of altering immunosuppression in an effort to improve glycemic control in patients with NODAT remains controversial [130,133]. Matas et al. compared the outcomes in NODAT kidney transplant recipients and concluded that prevention of acute rejection was more important than prevention of NODAT in preserving long-term kidney function [136]; therefore a potential benefit of avoiding or reversing NODAT by a change of immunosuppressants (reducing or discontinuing corticosteroids or calcineurin inhibitors) must be weighed against the risk of precipitating acute or chronic rejection [130,135].

TABLE 3.2 Risk factors that predispose kidney graft recipients to new-onset diabetes mellitus after transplantation.

Nonmodifiable risk factors

- Advanced age
- Male gender
- Nonwhite ethnicity
- Family history of diabetes
- Impaired glucose tolerance before transplantation

Modifiable risk factors

- Overweight and obesity
- Posttransplantation weight gain
- Hepatitis C virus infection
- Cytomegalovirus infection
- Immunosuppressive agents
  - Glucocorticoids
  - Calcineurin inhibitors (cyclosporine and to a greater extent tacrolimus)
  - Sirolimus and everolimus

Treatment of diabetes mellitus in diabetics with chronic kidney disease

Target of treatments

At present, HbA1c blood concentration, which reflects average glucose plasma concentration over 8–12 weeks preceding the test, is widely used as a standard index for glycemic control in clinical practice in general population. However, the HbA1c blood concentrations may be interpreted erroneously in patients with CKD [137]. In CKD the lifespan of erythrocytes is shortened, and low HbA1c values may therefore be artificially low because of shorter exposure of erythrocytes to glycemia. Therefore HbA1c blood concentration underestimated poor glycemic control in CKD. Other possible markers of diabetes control monitoring (fructosamine and glycated albumin plasma concentrations) are also influenced by CKD-dependent factors. Both fructosamine and glycated albumin plasma concentrations depend not only on glucose concentrations but also on the proteinemia and protein turnover which might be influenced by nutritional status and degree of proteinuria [137].

The target HbA1c in CKD patients remains the subject of controversy. Experts from the European Renal Best Practice (ERBP) group suggest to achieve a target HbA1c value of 8.5 in patients with GFR of less than 45 mL/min/1.73 m^2 [138]. The KDIGO guidelines suggest that in CKD patients, the HbA1c blood concentration should be 7.0% or less to prevent microvascular complications [139]. Target over 7.0% should be recommended in CKD patients with comorbidities and risk of hypoglycemia (maintenance HD patients are in this group) [139]. The abovementioned expert opinion is based mainly on the results of metaanalysis of 10 studies (83,684 dialysis patients) [140]. In this metaanalysis, it was found that patients with a baseline HbA1c blood concentration of >8.5% are characterized by increased mortality (Hazard ratio-HR 1.14; 95% CI 1.09–1.19) when compared with patients with an HbA1c blood concentration of 6.5%–7.4%. An HbA1c blood concentration of <5.4% was also associated with an increased mortality risk (HR 1.29; 95% CI 1.23–1.35) [140]. Therefore there is no benefit of tighter glycemic control is assessed by an HbA1c of <6.5, whereas there was a clear risk for consequences of hypoglycemia episodes when glycemic control is tightened.

Drug management in diabetics with chronic kidney disease

Metformin

Metformin is the only biguanide currently available. It increases insulin sensitivity by activating hepatic and muscle isoforms of adenosine monophosphate—activated protein kinase [141]. This causes decreased hepatic glucose production and increased glucose utilization. Metformin is the first-line antidiabetic therapy in general population because it has a proven impact on all causes and cardiovascular mortalities [142,143]. Moreover, with metformin, modest weight loss can be achieved. Additional advantages of metformin therapy include a low risk of hypoglycemia and a minor, but beneficial, effect on abnormal lipid profiles [141]. Retrospective, observational studies suggest that patients treated with metformin experience slower progression of CKD as compared to those treated with sulfonylurea agents. These data indirectly suggest nephroprotective properties of metformin. Metformin is cleared by renal excretion, and consequently, metformin accumulates in CKD [144]. The most dangerous side effect of metformin is lactic acidosis [141]. Large observational studies focused on the incidence of lactic acidosis in metformin-treated patients suggest that the risk of this complication is low and comparable to the risk observed in patients who are treated with the other glucose-lowering agents. In one of the analyses, lactic acidosis was found with a frequency of 3.3 per 100,000 metformin users and 4.8 per 100,000 patients not using this drug. In the same paper, hypoglycemia was found in 60 out of each 100,000 patients treated with metformin and 110 per 100,000 who were using other drugs; severe hypoglycemia was 20 times higher in those who were treated with other drugs as compared to metformin users [145]. In the context of advanced kidney disease the risk of lactic acidosis, is increased for two reasons: on the one hand, metformin accumulates, and on the other, the renal clearance of lactate is decreased [141]. The degree of kidney disease at which metformin is strictly contraindicated remains controversial [144]. According to some manufacturers and guidelines bodies, it has been stated that the drug can be used when GFR decreases to the range between 30 and 60 mL/min. If GFR is between 30 and 44 mL/min, the initial dose should not exceed 50% of the maximum dose (i.e., 1000 mg/day), whereas in the GFR range of 45—59 mL/min, it may be used in a full dose of 2000 mg/day. Metformin is contraindicated when GFR falls below 30 mL/min and should be strictly avoided in dialysis patients, however. It is strongly advised to carefully monitor the kidney function in diabetic patients treated with metformin.

Sulfonylureas

Sulfonylureas enhance the pancreatic insulin secretion. As a result of increased plasma insulin concentration, weight gain and hypoglycemia are common side effects. The older sulfonylureas are predominantly metabolized in the liver to yield active metabolites which are cleared via the kidney along with unmetabolized drug [119,146]. In patients with kidney dysfunction, accumulation of the parent drug and of metabolites of some sulfonylurea compounds can lead to hypoglycemia. Consequently, these first-generation sulfonylureas should be avoided at least in patients with CKD. Among the second-generation sulfonylureas, glipizide and gliquidone are preferred in CKD patients. Glipizide and gliquidone are metabolized exclusively to the nonactive metabolites in the liver that are eliminated via the kidney [119,147]. Consequently, the risk of hypoglycemia in CKD patients is less. Nevertheless, because of the remaining risk of hypoglycemia, sulfonylureas should be used with caution even in mild to moderate CKD [119,146].

Pioglitazone

The only currently available TZD is pioglitazone. It is a selective agonists of the peroxisomal proliferator-activated receptor-γ (PPAR-γ) [119,146]. The ligands for these receptors are normally free fatty acids and eicosanoids. By activating PPAR-γ, it decreases leptin levels and certain ILs, while serum adiponectin increases [148]. TZDs act as a prandial glucose regulators and improve insulin sensitivity. The PROactive trial demonstrated that treatment with pioglitazone reduced the risk of cardiovascular events and the benefit was independent from renal function [149]. TZDs are predominantly metabolized and eliminated by the liver [119,146]. Consequently, no dose adjustments is necessary in patients with advanced kidney disease. A major TZDs side effect is sodium retention, particularly in patients with CKD, causing weight gain with reduction of hematocrit, edema, and even pulmonary edema, particularly in patients with heart failure [146]. Further side effects include higher fracture rates of distal bones in women and gastrointestinal side effects [146].

Meglitinides

The meglitinides, that is, repaglinide and nateglinide, are short-acting agents that bind to an ATP-dependent K channel on β-cell membranes (similar but not identical with that occupied by sulfonylurea); the resulting depolarization of pancreatic β cells causes Ca influx and increased insulin secretion [150,151]. Side effects of the meglitinides include hypoglycemia and weight gain. One of the significant advantages of meglitinides is their safe administration in CKD patients, because these drugs are mainly excreted by hepatic clearance [146]. Repaglinide seems to be safer than nateglinide. A minor amount of nateglinide, together with its active metabolite, is excreted in the urine [152]. Therefore, in advanced CKD, nateglinide treatment still increases the risk of hypoglycemia.

Glucagon-like peptide 1 agonists

The two main incretins secreted in the upper small intestine are glucagon-like peptide 1 (GLP-1) and glucose-dependent insulinotropic peptide [119]. Gut hormones have been shown to play an important role in whole-body glucose homeostasis by suppressing meal-related glucagon secretion, delaying gastric emptying, and inducing satiety [152]. As the GLP-1 effect is diminished in type 2 diabetics, administration of exogenous GLP-1s (liraglutide, exenatide, and dulaglutide) is a therapeutic option [153]. Liraglutide is not excreted by the kidney [154]. Therefore dosing does not need any adjustment until the GFR value falls down below 30 mL/min. When GFR is lower than 30 mL/min/1.73 m^2, the drug is not contraindicated, but there is limited experience in this range of GFR. Liraglutide should not be prescribed in patients with eGFR <15 mL/min/1.73 m^2 and during dialysis therapy [154]. In the LEADER trial, it was demonstrated that this drug decreased the mortality rate [155]. Another GLP-1 agonist exenatide is excreted by the kidneys. If GFR is higher than 50 ml/min, the dose does not need adjustment. Dose titration is recommended when GFR is in the range of 30–50 mL/min [153]. Dulaglutide dose adjustment is not necessary across the whole GFR range except below 30 mL/min [156]. This drug is now not recommended for use in CKD patients with GFR of less than 30 mL/min, mostly due to limited experience in this group of patients [156].

Dipeptidyl-peptidase 4 inhibitors

The abovementioned incretins, including GLP-1, are rapidly degraded by the enzyme DPP-4. The effort to inhibit this enzyme led to the development of a new class of antiglycemic agents, DPP-4 inhibitors such as sitagliptin, linagliptin, and vildagliptin [151,157]. They pose no intrinsic risk of hypoglycemia. Sitagliptin is predominantly excreted in urine and accumulates in CKD patients. Despite precautions suggested by the manufacturer for CKD patients, the drug was generally well tolerated and effective in improving metabolic control of type 2 diabetes CKD patients [158]. Vildagliptin is also safe and effective in CKD, despite the fact that the drug is metabolized by the kidneys and excreted in urine. When doses are reduced, they can still be used even in an advanced CKD [159]. The same applies for saxagliptin. DPP-4 inhibitors are considered to be safe and effective across all stages of CKD (includes patients treated with dialysis in which the dose should also be reduced) [157].

Acarbose

Acarbose inhibits α-glucosidase activity that leads to the inhibition of the hydrolysis of oligo-, di-, and trisaccharides to glucose and other monosaccharides. Therefore this drug reduced the postprandial increase in blood glucose [160]. The increased delivery of carbohydrates to the colon frequently causes side effects, for example, flatulence, bloating, abdominal pain, and diarrhea, rendering patient management difficult and reducing compliance [161]. In the context of renal impairment, acarbose in individuals with an eGFR less than 25 mL/min is not recommended [157].

Sodium–glucose cotransporter type 2 inhibitors

Sodium–glucose cotransporter type 2 inhibitors (SGLT2i) reduce glucose tubular reabsorption and therefore induce glucosuria [162]. Moreover, these drugs by reducing sodium tubular reabsorption induce natriuresis [162,163]. Therefore SGLT2i act as diuretics. These drugs also decrease body weight and reduce blood pressure [164]. In most studies, it was shown that SGLT2i significantly decrease cardiovascular morbidity and mortality and all-cause mortality in type 2 diabetes patients [162–164]. Moreover, these drugs also disclose by nephroprotective properties [162]. SGLT2i activate the tubulo-glomerular feedback: the increased sodium load at *macula densa* triggers constriction of the afferent arteriole, thus reducing intraglomerular pressure and hyperfiltration. The treatment with SGLT2i should not be initiated in patients with GFR of less than 60 mL/min/1.73 m^2 but might be continued till eGFR is over 45 mL/min/1.73 m^2. As was shown in DERIVE study, dapagliflozin was effective in the reduction of HbA1c, fasting blood glucose, body weight, and systolic blood pressure also in patients with eGFR ranging between 45 and 59 mL/min/1.73 m^2 [165,166]. Moreover, it is worth to state that the major studies with SGLT2i: EMPA-REG (with empagliflozin) and CANVAS and CREDENCE (with canagliflozin) enrolled some patients with eGFR between 30 and 60 mL/min/1.73 m^2 [167–170]. The Federal Drug Administration and European Medicines Agency have approved the continued use of canagliflozin in patients with a urinary albumin-to-creatinine ratio of 300 mg/g and eGFR less than 30 mL/min/1.73 m^2until renal replacement therapy [171].

Insulin

The use of insulin, human or analogs, is recommended in type 2 diabetic patients with advanced CKD and severe uncontrolled hyperglycemia. Another more theoretical background is that in these catabolic patients the anabolic effect of insulin may be desirable. No clinical evidence is available to decide the optimal timing to start insulin treatment or which particular insulin regimen should be preferred in advanced CKD.

In recent years, a number of insulin analogs have been marketed. These newer insulins were developed by modifying the structure of the insulin molecule to alter the pharmacokinetic properties. Based on the data from a limited number of small studies, specific insulin analogs are effective and safe for patients with CKD [172,173]. The major side effects of insulin include weight gain and risk of hypoglycemia. Dose adjustments are often required to minimize the risk of hypoglycemia, especially with individuals on dialysis [146]. In patients without kidney disease and who are given subcutaneous exogenous insulin, up to 80% of insulin is cleared by the kidneys. As GFR falls below 20 mL/min, the kidneys are no longer able to efficiently clear insulin, resulting in prolonged insulin half-life and an increased potential for hypoglycemia [174]. The American College of Physicians recommended (1) a 25% decrease in the insulin dose when the GFR is decreased to between 50 and 10 mL/min and (2) a 50% decrease when GFR decreased below 10 mL/min [175]. In addition, once maintenance dialysis is initiated, the insulin resistance seen in CKD is often improved. resulting in reduced doses of insulin. Insulin requirements are often substantially decreased in anorectic patients with advanced CKD. Other factors that may contribute to changes in the need for exogenous insulin include reduction in renal gluconeogenesis, uremia-induced anorexia, and weight loss. In fact, one-third of the patients with type 2 diabetes no longer require insulin after 1 year of HD therapy [176]. Therefore, when these patients are treated with insulin, it is imperative to monitor blood glucose concentrations and to adjust the dose as needed to avoid hypoglycemia.

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CHAPTER

4

Altered lipid metabolism and serum lipids in chronic kidney disease

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The nonnephrotic chronic kidney disease (CKD) and end-stage renal disease (ESRD) results in marked reductions of lipoprotein lipase (LPL) and very-low-density lipoprotein (VLDL) receptor in skeletal muscle and adipose tissue, downregulation of hepatic lipase, LDL receptor–related protein (LRP), Apolipoprotein A1 (ApoA-1) and lecithin–cholesterol acyltransferase (LCAT) in the liver, upregulation of acyl-CoA cholesterol acyltransferase (ACAT) in the liver, renal, and arterial tissues, reduction of plasma high-density lipoprotein (HDL), oxidative modification of LDL and HDL, and impaired antioxidant, antiinflammatory, and reverse cholesterol transport capacities of HDL. Together these abnormalities lead to impaired clearance of chylomicrons and VLDL, accumulation of proinflammatory and atherogenic chylomicron and VLDL remnants, formation of small dense LDL, hypertriglyceridemia, and reduced availability of lipid fuel for energy production and storage. These events contribute to systemic inflammation, accelerated atherosclerosis, cachexia, and impaired exercise capacity. Plasma cholesterol is usually within or below the normal limits and only occasionally elevated in patients with ESRD or nonnephrotic CKD. This accounts for the reported failure of the randomized clinical trials of cholesterol-lowering agents to reduce the risk of adverse cardiovascular outcomes and overall mortality in hemodialysis patients.

Introduction

During the last three decades the burden of CKD has dramatically increased worldwide, consuming a disproportionate share of the health-care resources. CKD is associated with the triad of oxidative stress, inflammation, and dyslipidemia that are causally interconnected and form a vicious circuit that drives progression of kidney disease and promotes cardiovascular disease, cachexia syndrome, anemia, and many other complications. This chapter is intended to provide an overview of the features and mechanisms of CKD-associated dyslipidemia and its role in amplification of inflammation and oxidative stress, disturbance of energy metabolism, progression of renal disease, cardiovascular, and other complications.

Plasma lipid and lipoprotein profile in chronic kidney disease/end-stage renal disease patients

Dyslipidemia in patients with nonnephrotic CKD and ESRD patients maintained on hemodialysis is characterized by hypertriglyceridemia, elevated plasma concentrations of VLDL, intermediate-density lipoprotein (IDL) and chylomicron remnants, accumulation of oxidized lipids and lipoproteins, and low plasma concentration of ApoA-1 and HDL cholesterol (HDL-chol) [1–6]. Unlike patients with heavy proteinuria who have hypercholesterolemia, serum-cholesterol and LDL-cholesterol values are frequently within or below the normal limits in the majority of hemodialysis-treated ESRD patients and CKD patients without nephrotic range proteinuria. In addition, LDL in these patients consists of highly atherogenic small dense particles that contain abnormal levels of residual triglycerides [7–10]. Finally, lipoprotein(a) [Lp(a)] plasma concentration

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particularly its low-molecular forms is elevated and contributes to the risk of cardiovascular events in CKD and ESRD patients [11–14].

Conditions that modify lipid profile in chronic kidney disease/end-stage renal disease

Several conditions significantly modify lipid profile in CKD or ESRD populations. These include dialysis modality (i.e., hemodialysis vs peritoneal dialysis), lipid-altering drugs (e.g., statins, fibrates, calcineurin inhibitors, steroids, and rapamycin), preexisting genetic disorders of lipid metabolism, and malnutrition and inflammation. In addition, by acting as a bile acid sequestrant, the commonly prescribed phosphate-binding resin, sevelamer, lowers plasma cholesterol concentration. Likewise, inflammation, which is a common feature of ESRD, can lower serum total cholesterol and further suppress HDL-chol levels. In contrast by simulating nephrotic syndrome [15,16], peritoneal dialysis, which results in substantial losses of proteins in the peritoneal dialysate effluent, can increase plasma LDL and total cholesterol concentrations. In addition, influx of large quantities of glucose from the peritoneal dialysis fluid can further raise plasma triglyceride levels in patients maintained on peritoneal dialysis.

The nature and mechanisms of chronic kidney disease–induced lipid abnormalities

High-density lipoprotein metabolism and function

HDL is a potent antioxidant, antiinflammatory, antithrombotic, and antiatherogenic component of the plasma. HDL protects against foam cell formation and atherosclerosis by promoting the efflux and preventing the influx of cholesterol in the macrophages in the artery wall. The combination of oxidative stress, structurally abnormal LDL, and the overabundance and prolonged plasma residence time of IDL and chylomicron remnants in CKD results in oxidation of LDL, lipoprotein remnants, and phospholipids. Once oxidized, these particles stimulate expression of scavenger receptors [e.g., oxidized LDL receptor-1 (LOX-1) and scavenger receptor A-1 (SRA-1)] in macrophages and resident cells in the artery wall. The scavenger receptors then engulf these oxidized lipids and lipoproteins, a process that is central to foam cell formation and atherosclerosis.

Normal HDL mitigates influx of lipids and lipoproteins in the macrophages by preventing or reversing lipid peroxidation via its potent antioxidant enzymes, that is, paraoxonase-1 (PON-1) and glutathione peroxidase (GPX). In addition, by raising endothelial production of nitric oxide and inhibiting release of chemokines, normal HDL limits monocyte adhesion and infiltration in the artery wall. Via these actions, normal HDL mitigates foam cell formation by limiting influx of cholesterol and inhibiting migration of immune cells into the arterial vessel wall. The other important and well-known mechanism of antiatherogenic action of HDL is reverse cholesterol transport reverse cholesterol transport (RCT) that involves extraction of surplus cholesterol and phospholipids from the lipid-laden cells and their disposal in the liver. The HDL-mediated RCT involves the following steps: (1) binding of the nascent, cholesterol ester (CE)-poor HDL to the adenosine triphosphate (ATP)-binding cassette transporter A-1 (ABCA-1) that is the gateway of cholesterol efflux on the surface of the target cell. HDL binding to ABCA-1 triggers deesterification of intracellular CE leading to release of free cholesterol and its migration to the cell surface and from there to the surface of HDL. (2) Reesterification of free cholesterol on the surface of HDL by LCAT that is an essential component of HDL complex. Due to its hydrophobic property, CE moves into the core of HDL, a process that by sustaining a favorable concentration gradient maximizes the uptake of cellular cholesterol and maturation of HDL to a CE-rich spherical particle. (3) Once matured, HDL detaches from the cell surface and travels to the liver where it binds to the scavenger receptor B-1 (SRB-1) that is expressed on the hepatocytes and serves as a docking receptor for the mature HDL. Binding to SRB-1 facilitates disposal of the HDL's CE cargo in the liver and clearance of its phospholipid and triglyceride by hepatic lipase. Once emptied, HDL detaches from hepatocyte and is released into the circulation. In contrast to the CE-rich HDL, CE-poor HDL particles have low affinity for SRB-1 and a high affinity for binding to the endocytic receptor (ATP synthase beta) that is expressed on hepatocytes and mediates removal and degradation of these particles [17].

Effect of chronic kidney disease on structure and function of high-density lipoprotein

As described in comprehensive reviews [5,18], CKD has a profoundly negative effect on the concentration, structure and antioxidant, antiinflammatory, and reverse cholesterol transport activities of HDL [19–23]. This is primarily due to (1) downregulation of hepatic biosynthesis and reduced plasma level of ApoA-1 that is the main protein component of HDL, the ligand for the HDL's loading and unloading receptors (ABCA-1 and SRB-1, respectively), and the principal carrier of HDL's lipid cargo [23–25]. The deficiency of ApoA-1 plays an important part in HDL deficiency and dysfunction in CKD. (2) The other important cause of CKD-associated HDL deficiency and dysfunction is reduced plasma concentration and enzymatic activity of LCAT that is due to the CKD-induced reduction of its hepatic production [26,27] and urinary losses in nephrotic syndrome [28]. The acquired LCAT deficiency in CKD plays a major role for the depressed HDL-mediated RCT, impaired HDL maturation, and reduced plasma HDL-chol, which collectively contribute to the atherogenic diathesis in this population. (3) CKD results in diminished plasma activity and concentration of paraoxonase and GPX [21,23] and elevation of myeloperoxidase [29], which contribute to the reduction of antioxidant capacity of HDL, thereby limiting its ability to prevent/reverse oxidation of LDL and remnant lipoproteins. Moreover, deficiency of the HDL's antioxidant enzymes heightens susceptibility of ApoA-1 to oxidative modification that limits the binding affinity of HDL to ABCA-1 and, thereby, negatively affects RCT [30]. (4) CKD results in diminished antiinflammatory capacity of HDL [4,5] that normally protects against plaque formation by raising nitric oxide production and inhibiting endothelial cell activation and monocyte adhesion and infiltration. (5) When present, nephrotic proteinuria results in marked reduction of hepatic HDL docking receptor (SRB-1) protein abundance, but not its transcript [31]. This can interfere with the HDL-mediated RCT by limiting disposal of HDL's cholesterol cargo. The observed reduction in hepatic SRB-1 protein abundance is due to downregulation of the adapter molecule, PDZ domain containing 1, which is essential for the transport and anchoring of the receptor to the hepatocyte plasma membrane [29]. (6) Deficiency of the hepatic HDL docking receptor, SRB-1, is compounded by upregulation of HDL endocytic receptor (beta chain ATP synthase) in CKD with, but not without, heavy proteinuria [30,31]. This can contribute to the HDL deficiency by raising its catabolism. (7) Oxidative modification of HDL that diminishes its ability to promote cholesterol efflux by limiting its binding affinity for ABCA-1 [29]. (8) Apolipoprotein M (ApoM) is another HDL-bound apolipoprotein that plays a role in the pre-Beta-HDL formation and facilitates cholesterol efflux from macrophages [32]. Plasma ApoM level is reduced and its deficiency contributes to cardiovascular complications in patients with advanced CKD [33]. (9) The HDL content of plasmalogens (belonging to the phospholipids family) that enhance the antiapoptotic and antiatherogenic properties and cholesterol efflux capacity of HDL are reduced in ESRD patients [34]. And finally, (10) hypoalbuminemia that is common in patients with advanced CKD contributes to the reduction of HDL-chol. This is because albumin shuttles substantial amounts of free cholesterol from the peripheral tissues to the circulating cholesterol-poor HDL particles and as such when present, hypoalbuminemia impairs reverse cholesterol transport [35].

It should be noted that the rates of cholesterol extraction from peripheral tissues and its disposal in the liver by HDL determine serum concentration of HDL-chol and its protective properties. Therefore both impaired cholesterol uptake that is marked by low HDL-chol concentration and impaired unloading of HDL-chol cargo in the liver that is marked by abnormal elevation of HDL-chol concentration increase the risk of cardiovascular and other complications. In fact, Chang et al. [36] found a significant increase in mortality among subpopulation of ESRD patients whose HDL-chol levels exceeded 60 mg/dL. This finding indicated that impaired capacity of HDL to unload its cholesterol cargo results in elevated HDL-chol and increased cardiovascular morbidity/mortality in a subpopulation of ESRD patients.

Together the abnormalities of metabolism, structure, and function of HDL contribute to the prevailing systemic inflammation and cardiovascular disease in the CKD population. The effects of CKD and ESRD on HDL metabolism and its adverse consequences are summarized in Fig. 4.1.

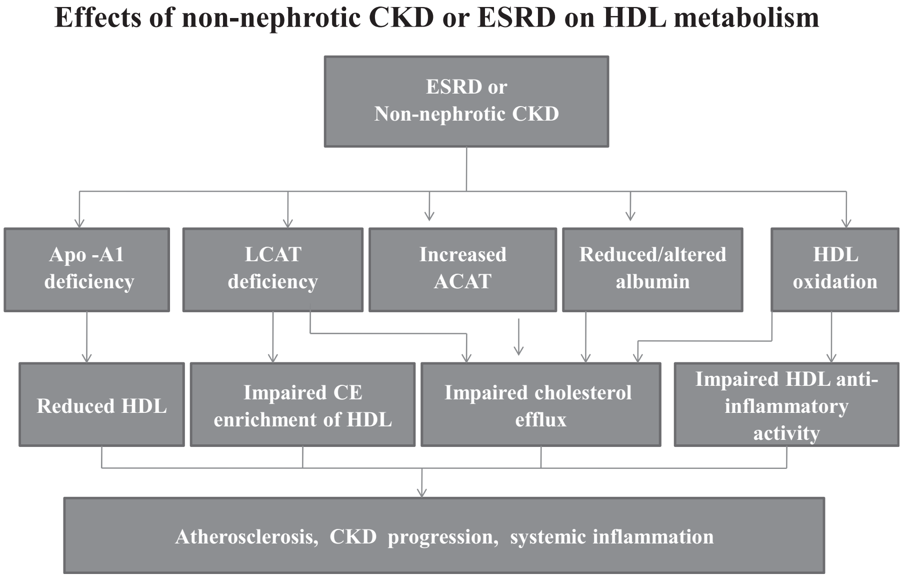
Effects of non-nephrotic CKD or ESRD on HDL metabolism
ESRD or Non-nephrotic CKD
Apo -A1 deficiency
LCAT deficiency
Increased ACAT
Reduced/altered albumin
HDL oxidation
Reduced HDL
Impaired CE enrichment of HDL
Impaired cholesterol efflux
Impaired HDL anti-inflammatory activity
Atherosclerosis, CKD progression, systemic inflammation

FIGURE 4.1 The nonnephrotic CKD or ESRD results in diminished production and depressed plasma levels of Apo-A1 and LCAT, upregulation of ACAT, reduced plasma concentration and structural modification of albumin, and oxidative modification of HDL. These events lead to reduced HDL cholesterol, impaired antioxidant, antiinflammatory, and reverse cholesterol transport capacities of HDL, which collectively promote atherosclerosis, systemic inflammation, and CKD progression. *ACAT*, Acyl-CoA cholesterol acyltransferase; *ApoA-1*, apolipoprotein A1; *CKD*, chronic kidney disease; *ESRD*, end-stage renal disease; *HDL*, high-density lipoprotein; *LCAT*, lecithin–cholesterol acyltransferase.

Effects of chronic kidney disease on very-low-density lipoprotein and chylomicron metabolism

VLDL and chylomicron are triglyceride-rich lipoproteins that deliver endogenous and dietary lipid fuels and construction material to the myocytes, adipocytes, and other cell types for production and storage of energy and incorporation in the cellular structures. Metabolism of VLDL and chylomicrons is markedly impaired in CKD. The nascent VLDL particles are assembled in the liver and nascent chylomicrons are packaged in the intestinal epithelial cells and released into the circulation. Once released into the circulation, the nascent VLDL and chylomicrons receive apolipoprotein E (ApoE) and apolipoprotein C (ApoC) from cholesterol-rich HDL-2 particles. Acquisition of ApoE and ApoC is essential for maturation and subsequent clearance of VLDL and chylomicrons in the peripheral tissues. However, scarcity of CE-rich HDL (caused by LCAT deficiency) in CKD severely impedes this essential process. Normally, chylomicrons and VLDL bind to the endothelial surface of the capillaries perfusing muscles and adipose tissues via ApoE and activate endothelial-bound LPL via ApoC-2. Once activated, LPL hydrolyzes the triglyceride contents of these particles. This leads to release of over 70% of free fatty acid contents of these particles for uptake by myocytes and adipocytes. The particles are then released into the circulation as VLDL remnants (also known as IDL) and chylomicron remnants. CKD results in significant reduction of LPL abundance and activity in skeletal muscle, adipose tissue, and myocardium [37–39]. This is accompanied by downregulation of the endothelium-derived adapter molecule, glycosylphosphatidylinositol-anchored binding protein 1 (GPIHBP1), which plays a critical role in LPL metabolism and function by anchoring LPL on the endothelium and binding chylomicrons [40]. Consequently, deficiencies of LPL and its adapter molecule, GPIHBP1, in CKD severely impair metabolism of VLDL and chylomicrons.

Chylomicron remnants and a portion of IDL are cleared from the circulation by LRP that is a large multifunctional endocytic receptor expressed in hepatocytes [41]. A study found significant downregulation of hepatic LRP in animals with CKD [42]. Given the central role of LRP in removing chylomicron remnants, its deficiency contributes to elevated plasma levels of these oxidation-prone atherogenic particles in CKD.

Under normal condition the great majority of IDLs are converted to LDL that is a CE-rich lipoprotein and is avidly cleared by the liver via LDL receptor. The transformation of IDL to LDL requires the removal of triglyceride cargo and CE enrichment of IDL. These events are catalyzed by CE transfer protein (CETP) and hepatic lipase. CETP mediates exchange of triglycerides for CE between IDL and CE-rich HDL2 particles and hepatic lipase catalyzes hydrolysis of the triglyceride and phospholipid contents of IDL. Although plasma CETP activity and concentration are normal in ESRD [43], the scarcity of CE-rich HDL limits the ability of CETP to fulfill its normal function. Moreover, CKD is associated with downregulation of hepatic lipase [44–46] that contributes to accumulation of IDL and formation of CE-poor, triglyceride containing small dense LDL. These abnormal LDL particles are highly oxidation prone and atherogenic and have low binding affinity for LDL receptor. Normally, a fraction of VLDL is cleared from the circulation via endocytosis by VLDL receptor that is expressed by myocytes and adipocytes [47]. A study in experimental animal model of CKD revealed significant downregulation of VLDL receptor expression in the skeletal muscle and adipose tissues [48,49]. This abnormality can potentially contribute to elevation of plasma VLDL and hypertriglyceridemia and thus compound the effects of LPL, hepatic lipase and LRP deficiencies, and impaired HDL maturation on VLDL and IDL metabolism in CKD. The effect of non-nephrotic advanced CKD or ESRD on metabolism of triglyceride-rich lipoproteins and its adverse consequences are summarized in Fig. 4.2.

Effect of chronic kidney disease on cholesterol metabolism

As mentioned earlier, plasma total cholesterol and LDL-cholesterol levels are frequently within or below the normal limits in most nonnephrotic CKD and ESRD patients receiving hemodialysis therapy. In addition, HMG-CoA reductase expression and activity are normal in the liver of animals with nonnephrotic CKD, induced by subtotal nephrectomy [50]. Moreover, hepatic expression of LDL receptor, HDL docking receptor and activity of the cholesterol 7-alpha hydroxylase, the enzyme responsible for conversion of cholesterol to bile acids are normal in CKD animals [51]. Despite having normal or subnormal plasma cholesterol and LDL-cholesterol levels and presumably normal cholesterol biosynthesis and cholesterol clearing capacities, the risk of atherosclerosis and cardiovascular disease is greatly increased in CKD patients. In fact, CKD animals exhibit accumulation of cholesterol in the artery wall and remnant kidney [51,52]. This is associated with and driven by oxidation of lipids and lipoproteins, upregulation of SRA-1 and LOX-1, and ACAT, the enzyme responsible for intracellular sequestration of CE and foam cell formation in the artery wall and diseased kidney [53–56]. These observations illustrate the critical role of oxidative stress and inflammation as opposed to elevated

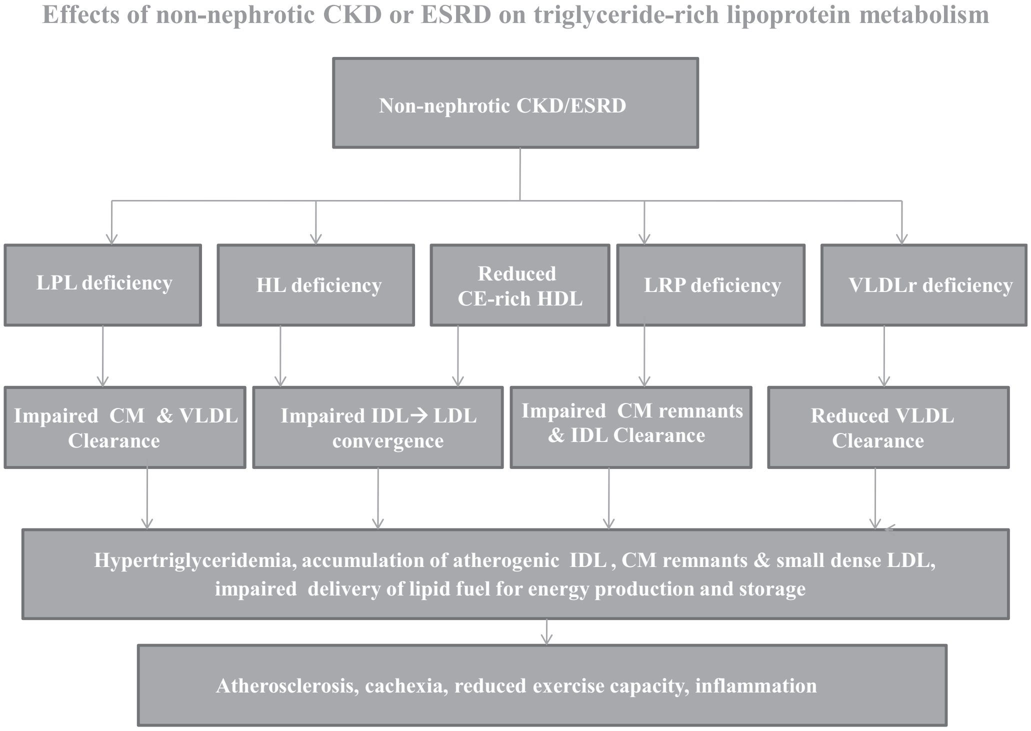
Effects of non-nephrotic CKD or ESRD on triglyceride-rich lipoprotein metabolism
Non-nephrotic CKD/ESRD
LPL deficiency
HL deficiency
Reduced CE-rich HDL
LRP deficiency
VLDLr deficiency
Impaired CM & VLDL Clearance
Impaired IDL→ LDL convergence
Impaired CM remnants & IDL Clearance
Reduced VLDL Clearance
Hypertriglyceridemia, accumulation of atherogenic IDL , CM remnants & small dense LDL, impaired delivery of lipid fuel for energy production and storage
Atherosclerosis, cachexia, reduced exercise capacity, inflammation

FIGURE 4.2 The nonnephrotic CKD or ESRD results in downregulation of skeletal muscle, adipose tissue, and myocardial LPL and VLDLr, HL, LRP and marked reduction of plasma CE-rich HDL. Together these abnormalities lead to impaired clearance of chylomicrons and VLDL, accumulation of oxidation-prone atherogenic chylomicron remnants and IDL, formation of small dense LDL, increased plasma triglyceride concentration, and reduced delivery of lipid fuel for energy production in myocytes and storage in adipocytes. Accumulation of the atherogenic chylomicron remnants and IDL and formation of small dense LDL promote atherosclerosis and systemic inflammation whereas reduced LPL- and VLDL receptor−mediated delivery of lipid fuel contributes to cachexia and reduced exercise capacity. *CE*, Cholesterol ester; *CKD*, chronic kidney disease; *ESRD*, end-stage renal disease; *HDL*, high-density lipoprotein; *HL*, hepatic lipase; *IDL*, intermediate-density lipoprotein; *LDL*, low-density lipoprotein; *LPL*, lipoprotein lipase; *LRP*, LDL receptor−related protein; *VLDL*, very-low-density lipoprotein; *VLDLr*, VLDL receptor.

plasma cholesterol or increased cholesterol biosynthesis as the cause of atherosclerosis in CKD. It is, therefore, not surprising that as described in the section on clinical trials, statins have proven ineffective in lowering the incidence of cardiovascular disease in the majority of ESRD patients maintained on hemodialysis. However, when present, preexisting hereditary hypercholesterolemia and nephrotic proteinuria compound the effect of renal insufficiency and cause hypercholesterolemia by raising cholesterol biosynthesis (upregulation of HMG-CoA reductase) and limiting cholesterol clearance (inducing LDL receptor and HDL docking receptor deficiencies).

The nature and mechanisms of adverse effects of lipid disorders in chronic kidney disease

Alterations of lipid metabolism have far-reaching consequences and contribute to numerous CKD-associated disorders and complications [53,57]. Some of these effects are briefly described in the following sections.

Inflammation and oxidative stress

As noted earlier, the CKD-induced constellation of LPL, hepatic lipase and LRP deficiencies, and impaired HDL function results in extended residence time and accumulation of IDL and chylomicron remnants in the plasma and formation of small dense LDL. The IDL, chylomicron remnants, and small dense LDL particles are exquisitely susceptible to oxidation, a phenomenon that is amplified by the prevailing oxidative stress and HDL deficiency/dysfunction in the CKD population. In fact, plasma concentration of oxidized LDL and lipid peroxidation products is markedly increased in patients and animals with CKD. Oxidized LDL and remnant particles promote inflammation by avidly binding LOX-1, SRA-1, and oxidized phospholipid receptors on monocytes and macrophages, thereby triggering release of proinflammatory cytokines. Riding in the circulating blood these particles can disseminate inflammation throughout the body. Likewise, through lipid peroxidation chain reaction, oxidized lipoproteins contribute to dissemination and amplification of oxidative stress that is a constant feature of CKD. Accordingly, dysregulation of lipid metabolism in CKD plays a part in the pathogenesis of systemic inflammation and oxidative stress that are constant features and major mediators of progression of CKD and its cardiovascular and many other complications [54].

Atherosclerosis and cardiovascular disease

CKD results in accelerated atherosclerosis and cardiovascular disease that are the main causes of death in this population [58–60]. In addition to the classic atherosclerosis, several other conditions contribute to cardiovascular disease in the CKD/ESRD population. These include arteriosclerosis, which is marked by stiffening of the arteries, endothelial dysfunction, vascular calcification, myocardial fibrosis, cardiomyocyte/capillary mismatch, dilated cardiomyopathy, and sudden cardiac death [61–65]. These disorders are mediated by hypertension, hypervolemia, phosphate retention, reduced nitric oxide availability (caused by oxidative stress and accumulation of NO synthase inhibitor, asymmetrical dimethylarginine), electrolyte abnormalities, myocardial fibrosis and ischemia (triggering arrhythmias), and drug toxicities, among other conditions. Atherosclerosis in CKD is primarily driven by the prevailing inflammation and oxidative stress [66,67] as opposed to elevated plasma cholesterol concentration or low HDL-chol level. In fact, observational studies have shown an association between low plasma cholesterol and highly elevated HDL-chol with increased risk of cardiovascular and overall mortality in ESRD population and a greater survival in those with higher serum total and LDL-cholesterol values [8,68]. It should be noted, however, that the association between higher plasma cholesterol levels with a lower mortality in ESRD patients is most likely related to the cholesterol-lowering action of systemic inflammation as opposed to the salutary effect of high-cholesterol concentrations.

Although elevated cholesterol in patients with familial hypercholesterolemia, chronic nephrotic syndrome, high dietary cholesterol, or other causes can lead to atherosclerosis and cardiovascular disease, accelerated atherosclerosis frequently occurs in the absence of hypercholesterolemia in patients with type 2 diabetes and patients with CKD and ESRD. This is not surprising since relatively small amounts of cholesterol are sufficient to form plaques capable of causing serious cardiovascular events by occluding coronary, cerebral, or peripheral arteries. Therefore disorders that increase influx and/or impair efflux of cholesterol in the macrophages can cause atherosclerosis and cardiovascular disease even when plasma cholesterol is within or below the normal limits. This is clearly illustrated by the failure of the cholesterol-lowering strategies to lower cardiovascular events in the randomized clinical trial of various statins in ESRD patients maintained on hemodialysis [69–71]. The primary mechanism of accelerated atherosclerosis in CKD/ESRD patients is most likely the oxidation of small dense LDL, chylomicron remnants and IDL, and their avid uptake by macrophages. The increased cholesterol influx is compounded by HDL deficiency and dysfunction, which limit reverse cholesterol transport in CKD. Consequently, the atherogenic process in highly inflamed CKD patients proceeds relentlessly regardless of plasma cholesterol level and despite the use of cholesterol-lowering agents.

Lipotoxicity and its role in progression of kidney disease

The prevailing oxidative stress in CKD results in accumulation of oxidized lipids and other compounds in the body fluids and tissues [72–77]. Macrophages and mesangial cells in the diseased kidney avidly engulf oxidized lipids and lipoproteins [77]. Accumulation of lipid in the renal tissue can promote progression of glomerular and tubulointerstitial lesions in metabolic syndrome and in chronic glomerular diseases [73,77–80]. In fact, progression of renal disease in the animals with CKD induced by subtotal nephrectomy is accompanied by heavy accumulation of lipids in the glomeruli and proximal tubular epithelial cells and in the artery wall [52] and accumulation of lipids in the nonadipose tissues can cause cellular injury and dysfunction [81] as seen in hepatic steatosis and atherosclerosis. Cellular lipid homeostasis is regulated by the balance between influx, efflux, synthesis, and catabolism of lipids. An imbalance in these pathways can result in lipid accumulation in macrophages, mesangial cells, vascular smooth muscle cells (VSMCs), and other cell types causing tissue damage. Influx of lipids into macrophages and mesangial cells is mediated by a number of receptors, including scavenger receptor class A (SRA-1), class B (CD36), and class E (LOX-1) [78,79]. Lipid accumulation in the wall of the aorta and remnant kidney in 5/6 nephrectomized rats is accompanied by marked upregulation of SRA-1 and LOX-1 [51,52], pointing to increased lipid influx in these tissues. Oxidized LDL and inflammatory cytokines stimulate expression of these receptors. This illustrates the causal link between oxidative stress and inflammation with accumulation of lipids in the macrophages and VSMCs in the artery wall and in the macrophages and mesangial cells in the renal tissue in CKD animals.

The development of glomerulosclerosis and progression of kidney disease is associated with proteinuria. Proximal tubular epithelial cells reabsorb filtered proteins, including lipid-carrying proteins such as albumin and ApoA-1 via megalin–cubilin complexes expressed on their apical membrane [79,80]. Glomerular proteinuria markedly increases the burden of reabsorbed filtered proteins and their lipid cargo causing expansion of the intracellular lipid pool in proximal tubular epithelial cells. In addition, interaction of protein-bound lipids with megalin−cubilin complexes activates several signal transduction pathways that trigger cellular apoptosis and release of proinflammatory and profibrotic mediators and thereby contributes to tubular atrophy, interstitial fibrosis, and inflammation [82]. In fact, proteinuria, glomerulosclerosis, tubulointerstitial fibrosis, inflammation, and accumulation of lipids in the proximal tubular epithelial cells in the remnant kidneys of rats 12 weeks after 5/6 nephrectomy were associated with marked upregulation of megalin−cubilin complexes [52]. These findings demonstrate the role of proteinuria in accumulation of lipid in the proximal tubules and the potential lipid-mediated tubular injury and interstitial inflammation and fibrosis.

Studies of the cholesterol efflux pathway in the remnant kidney tissue and artery wall have shown upregulation of ABCA-1 and activation of its upstream transcription factor, liver X receptor that is an intracellular sterol-sensing molecule [51,52]. This phenomenon represents the cellular response to elevated cholesterol burden in the arterial and remnant kidney tissues in CKD. The success of the upregulation of cellular cholesterol efflux pathway in unloading of the surplus cholesterol depends on HDL-mediated uptake and disposal of the lipid cargo. However, HDL-mediated reverse cholesterol transport is severely impaired in CKD. Several factors contribute to the reduction of HDL-mediated reverse cholesterol transport in CKD. These include diminished hepatic production and plasma concentration of ApoA-1 and LCAT as well as oxidative modification of HDL that can compromise the critical interaction between HDL and ABCA-1.

Studies of the de novo lipid biosynthesis have revealed marked suppression of cholesterol production machinery in the diseased kidney [52]. These findings substantiate excessive influx and impaired HDL-mediated efflux as opposed to increased local production as the cause of cholesterol accumulation in the renal tissue. However, fatty acid production machinery is upregulated and peroxisome proliferator−activated receptor (PPAR)-α-driven fatty acid catabolism is suppressed in the diseased kidney [52]. Upregulation of the fatty acid production system in the remnant kidney is driven by activation of carbohydrate response element-binding protein (ChREBP) that is an intracellular sensor of glucose. The activation of ChREBP and consequent increase in fatty acid synthesis in the remnant/diseased kidney is most likely driven by increased filtered glucose load per nephron occasioned by increased single-nephron glomerular filtration rate (GFR).

Activity of PPAR-α that is the master regulator of fatty acid catabolism is markedly reduced in the remnant/diseased kidney. In the normal kidney, PPAR-α is heavily expressed in the proximal tubules and medullary thick ascending limb of loop of Henle and is weakly expressed in mesangial cells [82]. PPAR-α regulates expression of genes involved in fatty acid catabolism, including liver type fatty acid−binding protein (L-FABP) and acyl-CoA oxidase (ACO). These proteins play a critical part in mitochondrial and peroxisomal beta oxidation of fatty acids. Earlier studies revealed significant downregulation of PPAR-α activity (nuclear translocation) and its target genes, L-FABP and ACO in the remnant kidneys of rats with CKD [52,83]. These findings unraveled yet another mechanism that contributes to increased lipid burden and lipotoxicity in the diseased kidney. Accordingly, increased production and depressed catabolism of fatty acids along with heightened influx and impaired efflux of cholesterol and neutral lipids contribute to accumulation of lipids in the diseased kidney. This is accompanied by significant upregulation of the enzyme ACAT1 that catalyzes esterification of cholesterol and sequestration of CEs in intracellular vesicles, a process that impedes HDL-mediated cholesterol efflux and leads to foam cell transformation [52]. In fact, a study demonstrated that administration of an ACAT inhibitor can ameliorate proteinuria and preserve residual renal function in this model [84] pointing to the role of ACAT in progression of renal disease.

There is little evidence that hyperlipidemia per se can cause kidney disease in the absence of preexisting renal disease or conditions that cause kidney disease. However, when present, hyperlipidemia can accelerate progression of preexisting renal disease and amplify the effect of conditions that can induce kidney disease. For instance, consumption of a high-cholesterol diet augments the development of glomerulosclerosis in rats with unilateral nephrectomy [85]. Similarly, induction of hypercholesterolemia with high-cholesterol diet increases the severity of proteinuria and glomerular lipid deposition in rats with CKD induced by subtotal nephrectomy [85]. Moreover, lipid-lowering strategies ameliorate renal injury in several animal models of CKD. For instance, administration of lovastatin has been shown to attenuate glomerular injury and albuminuria in Dahl salt-sensitive rats consuming high salt diet [86]. Likewise, administration of antihypertensive and cholesterol-lowering agents attenuated severity of histological lesions and the associated proteinuria in rats with nephrotoxic serum nephritis [87]. The salutary effects of lipid-lowering interventions in most animal models of CKD are associated with the reduction of inflammatory cell infiltration, fibrosis, and expression of proinflammatory and profibrotic mediators and consistently observed in different models of renal injury [88−91].

Nutrition and energy metabolism

In addition to causing hypertriglyceridemia and contributing to amplification of oxidative stress, inflammation, and cardiovascular disease, defective clearance of triglyceride-rich lipoproteins leads to impaired energy metabolism, reduced exercise capacity, cachexia, and malnutrition syndrome in patients with advanced CKD. By limiting the delivery of lipids to the adipocytes and myocytes, downregulation of LPL and VLDL receptor limits the availability of lipid fuel and construction material to the skeletal muscles and myocardium and adipose tissues in CKD [49]. This abnormality deprives the skeletal muscle and myocardium from free supplies of lipid fuel and as such can contribute to muscle weakness and myocardial dysfunction. Likewise, diminished delivery of fatty acids to the adipose tissue limits the long-term energy storage capacity and contributes to weight loss and cachexia in ESKD patients.

Treatment of chronic kidney disease—associated dyslipidemia

In light of the role of dyslipidemia in progression of CKD and the associated cardiovascular complications, interventions aimed at improving lipid metabolism can be important in the management of patients with CKD. A brief description of the available data on the efficacy of the currently available lipid-modulating drugs in the treatment of CKD-induced dyslipidemia is provided in the following sections.

Statins in primary prevention of cardiovascular disease in end-stage renal disease patients

Three large prospective randomized controlled clinical trials were conducted to address the efficacy of statin therapy in lowering the risk of cardiovascular mortality in ESKD patients maintained on hemodialysis. The first of these trials was the 4D (Die Deutsche Diabetes Dialyse) study [69] that enrolled 1255 hemodialysis patients with type 2 diabetes randomized to atorvastatin, 20 mg/d or placebo for 4 years. The study despite a significant decrease in serum LDL-cholesterol level showed no significant reduction of the risk of death from cardiac causes, nonfatal myocardial infarction (MI), and instead revealed a significant increase in the risk of a fatal stroke (95% CI 1.05–3.93) in the statin-treated group.

The second large trial termed "An assessment of Survival and Cardiovascular Events (AURORA)" was a double-blind, randomized, placebo-controlled, multicenter trial undertaken to compare the effect of rosuvastatin 10 mg/d versus placebo on cardiovascular morbidity and mortality in ESRD patients maintained on regular hemodialysis treatment [70]. A large number (2776) of patients 50–80 years of age on dialysis for at least 3 months were enrolled in this study from 25 countries. The primary endpoint was major cardiovascular events, including fatal and nonfatal MI and stroke; the secondary endpoints included all-cause mortality, revascularization, and death from cardiovascular and noncardiovascular causes; and the tertiary endpoints included changes in the baseline lipids and high-sensitivity C-reactive protein (hs-CRP). The mean baseline LDL-cholesterol values in the rosuvastatin (100 mg/dL) and placebo (99 mg/dL) groups were nearly identical. The mean duration of treatment and the mean length of follow-up were 2.4 and 3.2 years, respectively. A total of 1296 patients died, and 810 patients discontinued the treatment because of adverse drug reactions or renal transplantation during the study period. The LDL-cholesterol concentration fell by approximately 43% and hs-CRP decreased by 11.5% in the rosuvastatin group within the first year of the trial. However, despite marked reduction of cholesterol level in the rosuvastatin-treated group, no significant difference was observed in either mortality or primary or secondary endpoints between the two groups. Moreover, a significant increase in the rate of fatal hemorrhagic stroke was found in the rosuvastatin-treated patients with diabetes ($P = .03$), confirming the results of the 4D trial.

The third and the largest randomized primary prevention statin trial in CKD patients was the Study of Heart and Renal Protection (SHARP) [71]. This study differed from the 4D and AURORA trials since in addition to the dialysis patients it included a large cohort of CKD patients who did not require dialysis. A total of 9270 patients (3023 ESRD patients on maintenance dialysis and 6247 CKD patients not requiring dialysis) without history of MI or coronary revascularization were enrolled in this study. Patients were randomly assigned to receive simvastatin 20 mg/d with or without ezetimibe 10 mg/d or placebo. The median duration of follow-up was 4.9 years. Mean baseline LDL-cholesterol levels were 108 mg/dL in the entire group and 100 mg/dL in the dialysis subgroup. It was lowered by 30 mg/dL with simvastatin alone and by 43 mg/dL with simvastatin plus ezetimibe at 1 year. The study sought to investigate effectiveness of LDL-cholesterol reduction on major vascular events and the rate of progression of CKD in as yet dialysis-independent patients. The estimated GFR (eGFR) in the CKD groups averaged 27 mL/min/1.73 m^2. The primary endpoints were the occurrence of a major atherosclerotic event that included death due to coronary disease, MI, nonhemorrhagic stroke, or the need for revascularization procedures. The study revealed 17% reduction in major atherosclerotic events (relative risk

0.83; 95% CI 0.74, 0.94; log rank $P = .002$), 25% reduction in nonhemorrhagic stroke, 21% reduction in coronary revascularization, and a trend toward reduction in nonfatal MI in the entire simvastatin- and ezetimibe-treated arm. It should be noted, however, that cholesterol-lowering therapy did not significantly reduce either mortality rates or cardiovascular events in the dialysis-dependent ESRD patients enrolled in the SHARP trial. Therefore the results of the SHARP trial confirmed those of AURORA and 4D studies and the only reason for the salutary results reported for the entire enrolled population was the fact that the SHARP trial was weighted toward patients with less advanced CKD, in whom the underlying mechanisms of cardiovascular disease are more akin to that in the general population.

Holdaas et al. [92] conducted a multicenter, randomized, placebo-controlled trial in 2102 renal transplant recipients in which participants were randomly assigned to receive fluvastatin or placebo. The primary endpoint included major cardiac events (cardiac death, nonfatal MI, or coronary interventions). After an average follow-up of 5 years, fluvastatin significantly reduced serum LDL-cholesterol concentration by 32%. Although there were significantly fewer cardiac deaths or nonfatal MI [70 vs 104, 0.65 (0.48–0.88) $P = .005$] in the fluvastatin group than in the placebo group, the risk reduction for the primary endpoint [risk ratio 0.83 (95% CI 0.64–1.06), $P = .139$] did not reach statistical significance. Likewise, the incidence of coronary intervention procedures and other secondary endpoints were not significantly different between the fluvastatin and placebo-treated groups.

The negative results observed in trials of statins in hemodialysis patients contrast their salutary effects in reducing the risk of cardiovascular events in the general population [93]. As noted earlier, plasma cholesterol is within or below the normal limits in the majority of ESKD patients maintained on hemodialysis and the atherosclerosis and cardiovascular diseases in this population are primarily driven by oxidative stress, inflammation, HDL deficiency and dysfunction, impaired clearance of VLDL and chylomicrons, accumulation of IDL and chylomicron remnants, and formation of atherogenic small dense LDL. Since these abnormalities are not amenable to statin therapy, it is not surprising that treatment with these agents does not reduce the risk of cardiovascular disease in this population. However, when present, hypercholesterolemia can compound the risk of cardiovascular disease in this population in whom statin therapy can have salutary effects. This supposition was confirmed by a post hoc analysis of the 4D study [94] that demonstrated that atorvastatin significantly reduced the rates of adverse cardiovascular and overall outcomes in patients with the highest quartile of baseline LDL cholesterol (≥145 mg/dL, 3.76 mmol/L). No such benefit was observed in patients with the other quartiles of LDL-cholesterol at baseline. Consequently, it is possible that statin therapy is effective in hemodialysis patients with elevated serum LDL-cholesterol concentrations.

Statins in primary prevention of cardiovascular disease in nondialysis chronic kidney disease patients

Data derived from subgroup analysis of the secondary prevention trials have suggested that statins may lower the risk of adverse cardiovascular outcomes in patients with stages I–IV CKD [95]. Likewise, meta-analysis of data on 18,176 patients with CKD stages I–IV derived from five different studies showed a significant reduction (0.81) of the relative risk of all-cause mortality with statin therapy [96]. The prospective randomized trial designed to evaluate efficacy of statins in patients with mild CKD called “Prevention of Renal and Vascular Endstage Disease Intervention Trial” (PREVENT IT study) [97] enrolled 864 patients with microalbuminuria. The patients were randomized to fosinopril 20 mg/d, pravastatin 40 mg/d, or matching placebos and followed for 4 years. The study showed an insignificant reduction in the cardiovascular mortality and hospitalization for cardiovascular morbidity in the pravastatin-treated group. The reason for the disparity in response to statin therapy between the PREVENT IT study and the former two studies is unclear. One possible explanation is the difference in the magnitude of proteinuria among the study populations. Heavy proteinuria is frequently associated with hypercholesterolemia and increased risk of cardiovascular disease. Hypercholesterolemia in this condition is due to downregulation of hepatic LDL receptor and HDL docking receptor, which results in increased hepatic HMG-CoA reductase activity and cholesterol synthesis [15,31,98]. Therefore pharmacological inhibition of HMG-CoA reductase with statins in such cases can have salutary effect. Patients enrolled in the PREVENT IT study had microalbuminuria, whereas patients included in the former studies had stages I–IV CKD that usually encompasses a significant subset of patients with significant proteinuria who might benefit from statin treatment. In this context, ESKD patients maintained on chronic peritoneal dialysis experience significant daily losses of proteins in their peritoneal dialysate effluent that can cause hypercholesterolemia simulating nephrotic syndrome in functionally anephric individuals. Unlike the majority of hemodialysis patients who have normal or subnormal plasma cholesterol, majority of peritoneal dialysis patients have hypercholesterolemia [98] and may benefit from statin therapy.

Effect of statins on progression of kidney disease

The available data on the effect of statins on progression of kidney disease are primarily derived from secondary or post hoc analysis of the secondary prevention studies and a limited number of randomized clinical trials that have directly addressed this issue. The former studies were primarily conducted to determine the effect of statins on cardiovascular outcomes in patients with either preexisting heart disease or those at high risk of developing cardiac disease. Among these studies the Heart Protection trial showed a significantly lower rate of decline in GFR in simvastatin-treated compared to placebo-treated groups [99]. The post hoc analysis of data from GREACE (Greek Atorvastatin and Coronary-heart-disease Evaluation) study that compared atorvastatin with usual care in patients with coronary artery disease showed an approximately 5% decline in eGFR in untreated patients with dyslipidemia and coronary disease and normal renal function at baseline during the 3-year study period. Treatment with statin prevented the decline in estimated GFR and in fact resulted in an approximately 5% increase in eGFR in the treated arm [100]. The salutary effect of statin on renal function was more pronounced in the lower two quartiles of baseline GFR and with higher atorvastatin doses. The subgroup analysis of the CARE trial showed that pravastatin significantly slowed the rate of the decline in GFR by 2.5 mL/min/year in patients with GFR below 40 mL/min/1.73 m^2, but not in the study population as a whole [101]. The subanalysis of data from the "Treatment to New Targets" study in patients with coronary heart disease [102] revealed a significant improvement in estimated GFR over the 5-year study period.

As noted earlier, only a few randomized controlled trials randomized controlled trials (RCTs) have directly explored the impact of statins on renal function. Moreover, the majority of these studies were not placebo controlled and were limited in size or duration and used various statins alone or with other lipid-lowering agents. In a metaanalysis of 12 such studies, Fried et al concluded that statins may retard progression of renal disease and attenuate proteinuria [103]. Similarly, a metaanalysis of data from 27 controlled trials or crossover trials of statins (including close to 40,000 participants) that reported assessment of kidney function showed a significantly slower rate of annual decline in eGFR (1.22 mL/min/year) in the statin-treated participants [104]. The subgroup analysis of the data revealed that the salutary effect of statin therapy was statistically significant in participants with cardiovascular disease but not in those with glomerulonephritis, diabetic nephropathy, or hypertensive kidney disease. In addition to reducing the rate of decline in GFR, statin therapy modestly reduced proteinuria in this population. The efficacy of statin therapy in lowering proteinuria has been demonstrated in metaanalyses of data derived from 50 trials that included large numbers of CKD and transplant patients reported by Douglas et al. [105] and Strippoli and associates [106]. Unlike the other statins, rosuvastatin lacks antiproteinuric effects and can actually increase proteinuria. This is most likely because concentrations of rosuvastatin and its metabolites is elevated in the renal tissue where it can adversely affect the kidney especially when used in high doses as seen in the "Prospective Evaluation of Proteinuria and Renal Function in diabetic and non-Diabetic Patients with Progressive Renal Disease Trials" (PLANET I and II studies, respectively) trials [107]. These prospective trials were designed to examine the efficacy of a 12-month therapy with rosuvastatin (10 mg or 40 mg/d) and atorvastatin (80 mg/d) on progression of renal disease in diabetic and nondiabetic patients with CKD. The studies revealed reduced proteinuria and slower rate of decline in eGFR in atorvastatin-treated group but modest increase in proteinuria and greater decline in eGFR in rosuvastatin-treated arm, particularly in those receiving the higher (40 mg/d) dose.

Taken together the available data suggest that with the exception of rosuvastatin, statins can be beneficial in retarding progression of CKD especially in those with significant proteinuria. However, these agents should be used with caution as at high doses they can have adverse renal and extrarenal consequences. For instance, Deslypere and colleagues [107] reported that 10 out of 120 patients receiving a high dose of simvastatin (40 mg/d) developed proteinuria that regressed following discontinuation of the drug and reappeared with its reintroduction. The proteinuric effect seen with rosuvastatin and occasionally with other statins appears to be, at least in part, due to impaired proximal tubular reabsorption of filtered proteins. In fact, in vitro studies have shown dose-dependent inhibition of protein uptake by simvastatin, pravastatin, and rosuvastatin in cultured human renal proximal tubular epithelial cells [108].

Mechanisms of protective effects of statins in chronic kidney disease

The salutary effect of statins on progression of kidney disease is mediated by their cholesterol-lowering and cholesterol-independent actions. In this context, in vitro and in vivo studies have shown that elevated LDL and oxidized LDL can activate mesangial cells, raise matrix production, stimulate release of chemokines and TGF-β, recruitment of monocytes and their transformation into resident macrophages leading to mesangial matrix expansion, lipid deposition, and foam cell formation [109–112]. These effects are much more intense with the oxidized LDL [77,113] that as noted earlier is significantly increased in patients with CKD.

In addition to their cholesterol-lowering properties, statins can confer renal protection by several cholesterol-independent pleiotropic effects via improvement of endothelial function [114], protection of podocyte [115,116], antioxidant and antiinflammation actions [117,118], reduction of plasminogen activator inhibitor-1 (PAI-1) production [119], suppression of extracellular matrix accumulation [120], and inhibition of VSMCs, mesangial, and monocyte/macrophage proliferation [121–124]. The majority of the cholesterol-independent pleiotropic effects of statins mentioned earlier are due to reduced production of isoprenoids particularly farnesyl pyrophosphate and geranylgeranyl pyrophosphate that are the intermediary metabolites of mevalonic acid. Via isoprenylation or prenylation processes, these intermediary metabolites play a critical part in intracellular transport, membrane anchoring, and regulation of the activities of small guanosine triphosphate (GTP)-binding proteins such as Ras, Rho, Rac, Rap, and Ral [125–130]. These GTP-binding proteins transition between inactive GDP-bound and active GTP-bound forms. As extracellular signal transducers, the GTP-binding proteins regulate many important physiological and pathological functions [131]. The protective effects of statins in kidney disease may be partly due to inhibition of Ras and RhoA [132]. Rac1 that is an important GTP-binding protein plays an essential part in activation of NAD(P)H oxidase. NAD(P)H oxidase is a major source of reactive oxygen species (ROS) in the kidney, vascular tissue, and immune cells. Inhibition of Rac1 signaling by statins has been shown to reduce ROS production in albumin-treated proximal tubular epithelial cells and in high glucose-treated aortic endothelial cells [133,134]. In addition to reducing ROS production, statins have been shown to raise expression of heme oxygenase-1 that catalyzes degradation of heme and generation of the potent antioxidant, bilirubin [135,136]. Moreover, statins have been shown to increase GPX activity [137] and reduce LDL oxidation [138]. Thus by lowering ROS production and raising antioxidant capacity, statins can ameliorate oxidative stress.

Another cholesterol-independent mechanism by which statins may slow progression of CKD is their ability to attenuate inflammation. In fact, statin therapy has been shown to significantly lower serum CRP that is a proinflammatory and prothrombotic mediator. The observed reduction of CRP is partially independent from cholesterol-lowering effects of the drug [139,140]. In addition, statins lower the release of proinflammatory cytokines and chemokines, [141,142], inhibit mesangial cell and leukocyte proliferation and macrophage infiltration [143], lower expression of profibrotic mediators [144–148], and attenuate expression of leukocyte integrins and endothelial adhesion molecules [149–152]. Besides reducing proinflammatory factors, statins may raise the number of $CD4^{+}CD25^{+}$ regulatory T cells that can help to suppress inflammatory response [153].

In the vascular tissue, statins upregulate expression and activity of endothelial NO synthase [154], suppress the endothelin system [114,155], and attenuate the effects of angiotensin II (Ang II) by lowering AT1-receptor expression [156] and reducing Ang II-stimulated ROS production by inhibiting Rac1 [157]. In addition, by inhibiting PAI-1 production and raising tissue plasminogen activator expression, statins can modify the fibrinolytic balance in the vessel wall [158] and thereby lower the risk of cardiovascular events.

As noted earlier, hypercholesterolemia contributes to CKD progression, in part, by damaging the podocytes [159]. Statins have been shown to attenuate podocyte injury in the model of nephrotic syndrome induced by puromycin aminonucleoside that causes podocyte injury and apoptosis [104]. The protective effect of statins on podocytes appears to be mediated by a p21-dependent antiapoptotic pathway [160]. In fact, statin therapy has been shown to reduce the number of podocytes found in the urine of patients with chronic glomerulonephritis, suggesting diminished podocyte loss and injury by these agents [161].

Potential adverse effects of statins

Besides blocking the synthesis of cholesterol, statins block the production of important intermediary (e.g., farnesyl pyrophosphate and geranylgeranyl pyrophosphates) and alternative (i.e., dolichols and ubiquinone) by-products of mevalonate pathway. Given the important biological functions of these by-products, their diminished production can have adverse consequences. For instance, ubiquinone (coenzyme Q10) is critical for mitochondrial electron transport and oxidative phosphorylation and dolichols are involved in production of glycoproteins that are necessary for tissue growth. In addition, farnesyl pyrophosphate and geranylgeranyl pyrophosphate are necessary for prenylation of proteins, which is essential for intracellular trafficking of newly synthesized proteins between the endoplasmic reticulum and Golgi apparatus, gene transcription, and regulation of cell growth. Therefore by curtailing the availability of these products statins can potentially disturb oxidative phosphorylation, signal transduction, intracellular traffic, gene transcription, and production/regulation of structural proteins [162]. In fact, these unintended effects of statins are responsible for the well-known side effects of statins such as myopathy and liver injury and possibly other less recognized systemic complications. Theoretically, the antiinflammatory/immunosuppressive properties of statins that are beneficial in attenuating systemic inflammation may raise the incidence and severity of microbial infections that are a common cause of morbidity and mortality in advanced CKD. Interestingly, large randomized clinical trials of statins in the general population have consistently revealed significant reduction in cardiovascular but not the overall mortality [163–165]. These observations indirectly imply that statins may increase mortality from noncardiovascular events probably as a result of the cholesterol-independent effects of these agents particularly when used at high doses.

Taken together statins seem to have salutary effects in CKD and ESKD patients with elevated, but not normal serum cholesterol. Among the available statins, those with minimal renal metabolism/excretion are preferable in CKD patients. Given their various side effects, the lowest effective dose should be used in this population.

Peroxisome proliferator–activated receptor-α agonists

PPAR-α agonists (fibrates) lower serum triglyceride by upregulating LPL and apoA-V and inhibiting apoC-III and increase HDL-chol by raising apoA-1 and apoA-2 expressions. Since hypertriglyceridemia and HDL deficiency are common features of CKD, PPAR-α agonists could be potentially useful in the management of CKD-induced dyslipidemia. A clinical trial of the PPAR-α agonist, gemfibrozil, showed a significant reduction of serum triglyceride, a significant increase in serum HDL-chol and lower incidence of coronary death and nonfatal MI in patients with mild-to-moderate CKD and coronary disease and low HDL-chol level [166]. However, the treatment did not alter the rate of the decline in kidney function. Instead, the drug tended to raise the risk of sustained elevations of serum creatinine in individuals with or without CKD [167,168]. Moreover, the safety and efficacy of these compounds in patients with severe renal disease remains unclear. These concerns have limited the utility of these compounds in the CKD population. Since no dose adjustment is needed for reduced GFR in patients with CKD, the National Kidney Foundation clinical practice guidelines (K/DOQI; 2003) recommended gemfibrozil as the fibrate of choice for the management of dyslipidemias in patients with kidney disease. However, the National Lipid Association has recommended a 50% reduction in the dose of gemfibrozil for patients with GFR below 60 mL/min/1.73 m^2 and avoidance of all fibrates in patients with GFR less than 30 mL/min/1.73 m^2. Fluvastatin is the only statin, the plasma levels of which are not increased when combined with gemfibrozil; therefore this combination may be preferred in CKD patients with mixed dyslipidemia [168]. It should be noted that when used concomitantly with statins, fibrates elevate serum level of statins most likely by interfering with the glucuronidation pathway of statin metabolism [168]. The exception is fenofibrate, which does not interfere with statin metabolism. However, major dose reduction is necessary when fenofibrate is used in patients with reduced GFR and the drug should be avoided in patients with GFR below 15 mL/min/1.73 m^2.

Niacin

At low doses, niacin can raise serum HDL-chol and at high doses it can simultaneously increase serum HDL-chol and reduce serum LDL, triglyceride, and Lp (a) levels. In addition, niacin has antioxidant and anti-inflammatory properties that may further enhance its ability to retard progression of renal disease and atherosclerosis. In fact, animal studies have shown significant attenuation of oxidative stress and lipotoxicity in CKD rats with long-term niacin administration [169,170]. Unfortunately, widespread clinical use of niacin in CKD patients has been limited in part due to its poor tolerability. One of the most common side effects of niacin and related compounds is flushing of the skin that is due to prostaglandin-mediated vasodilation and occurs in more than 80% of patients consuming regular crystalline preparations. The flushing can be attenuated by aspirin taken prior to each dose, use of the drug after meals, or use of the extended-release formulation. The other side effects of niacin include hepatotoxicity, hyperuricemia, and hyperglycemia. Hepatotoxicity that was relatively common with the older generation of sustained-release formulations seems to be uncommon with extended-release niacin. Finally, niacin can raise serum glucose level that may be of concern when prescribed for the diabetic patients. However, the glycemic effect of niacin is dose-dependent and is insignificant at low doses.

Cholesterol ester transfer protein inhibitors

CETP inhibitors markedly raise HDL-chol concentration by inhibiting CETP-mediated exchange of CE for triglycerides in the circulation. The clinical trial of the first product in this class, torcetrapib, was prematurely halted because contrary to expectations the drug increased the adverse cardiovascular outcomes despite marked increase in plasma HDL [171]. Although this phenomenon was attributed to a slight increase in blood pressure observed in the treated group, we believe that despite markedly raising plasma HDL-chol, CETP inhibitors may worsen cardiovascular outcomes in some patients since the increase in HDL-chol in this case is not due to enhanced removal of surplus cholesterol from the artery wall, kidney, or other tissues. Rather, it is merely due to inhibition of CETP-mediated transfer of CE from HDL to IDL/LDL in exchange for triglycerides in the circulation. In fact, by limiting the conversion of IDL to LDL and formation of CE-rich LDL, inhibition of CETP might lead to accumulation of atherogenic IDL and formation of small dense LDL, events that can accelerate atherosclerosis and intensify inflammation. Subsequently, results of several RCTs evaluating the impact of CETP inhibition on cardiovascular outcomes were similarly disappointing [172–174]. However, as noted earlier, CETP is markedly elevated in patients with nephrotic proteinuria. It is conceivable that low doses of CETP inhibitors may have salutary effect in patients with nephrotic syndrome.

Acyl-CoA cholesterol acyltransferase inhibitors

These drugs inhibit the intracellular enzyme, ACAT, which is a key factor in cholesterol metabolism. ACAT catalyzes esterification of free cholesterol to CE for incorporation in VLDL in the liver and chylomicrons in the intestine and for sequestration in intracellular vesicles in macrophages, VSMCs, and mesangial cells. The latter is the principal step in foam cell formation and an impediment to reverse cholesterol transport that depends on migration of free cholesterol from cytoplasm to plasma membrane for removal by HDL. Increased ACAT activity augments cholesterol synthesis by the liver and impedes HDL-mediated removal of cholesterol in the peripheral tissues. Consequently, pharmacological inhibition of ACAT can enhance HDL-mediated reverse cholesterol transport, raise plasma HDL-chol and reduce hepatic cholesterol production, events that can have significant protective impact on cardiovascular disease and potentially CKD. However, increased ACAT activity protects the cholesterol-loaded cells against disruption and death caused by high levels of free cholesterol. This is because due to its amphipathic properties, free cholesterol accumulates in the cellular membranes and when present in excess quantities it compromises the stability and physical properties of cell membranes. Therefore by raising intracellular free cholesterol in cholesterol-loaded cells, ACAT inhibitors can cause disruption of plasma membrane in resident macrophages leading to release of proteolytic enzymes and tissue factor, plaque rupture, and thrombosis. In fact, due to adverse cardiovascular outcomes, a large clinical trial of avasimibe that is a potent ACAT inhibitor was halted [175]. It is of note that in a series of studies the authors found a marked increase in ACAT expression and activity in the liver, remnant kidney, and arterial wall in animals with nephrotic syndrome [176] and chronic kidney insufficiency [56]. We subsequently found significant improvement in proteinuria, renal function, and plasma lipid profile with the administration of ACAT inhibitor, avasimibe, in both conditions [84,176]. It is, therefore, conceivable that low doses of ACAT inhibitors might have potential salutary effects on progression of renal disease in patients with nephrotic proteinuria lacking atherosclerosis.

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CHAPTER

5

Energy metabolism and requirements in chronic kidney disease

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Introduction

Regulation of energy balance is dependent on a complex set of mechanisms that are perturbed by chronic kidney disease (CKD), its underlying causes, and the therapies used in its treatment [1]. Patients with CKD face a number of challenges to their nutritional balance that produce adverse changes in nutritional status, including uremia-induced wasting disorders, dialysis-related nutrient losses, and factors such as acidosis, insulin resistance, and chronic inflammation that promote hypermetabolism [2,3]. Very low physical activity in CKD patients is another challenge that also affects energy balance [4]. Nutrition management is, therefore, one of the most important interventions to optimize nutritional status before and after the inauguration of renal replacement therapy, possibly to slow CKD progression, and to prevent and manage uremic toxicity and other complications and comorbid conditions [5,6]. An essential component of effective nutrition management is the determination of energy requirements that considers all the components of energy balance that can be affected by CKD [1], as illustrated in Fig. 5.1. This review presents the current information that integrates previous knowledge with a specific emphasis on energy balance and requirements in CKD. Recommendations related to energy balance in CKD from the recently released 2019 KDOQI (Kidney Disease Outcomes Quality Initiative)/Academy of Nutrition and Dietetics Clinical Practice Guidelines on Nutrition in Kidney Disease [6] are included in this review.

Energy balance

The human body cannot destroy or produce energy; it takes in energy from food, converts it into usable forms to perform life functions, and then passes it on to the environment [7,8]. The human body loses energy continuously to the environment in the form of heat; to sustain life, this energy must be restored. The source of this energy is the available energy in the highly structured carbon bonds in food, namely, carbohydrate, fat, and protein, which is extracted through oxidation. When a nutrient is oxidized, a part of its energy is thermodynamically obligated for conversion to heat since the heat energy content of the metabolic end products is greater than the available or chemical-free energy content of the initial nutrient. The amount of heat lost is not large, with approximately 95% of ingested energy available as free energy. The conversion of food energy into usable high-energy compounds (such as adenosine triphosphate, ATP) is not very efficient, with more than half of potentially available free energy lost to the environment as heat. This heat loss is essential since it is the basis for the unidirectional nature of metabolic pathways and their regulators. When hydrolysis of ATP is coupled with other reactions, energy retained in ATP can be transferred to other chemical compounds or transformed into mechanical or electrical energy. ATP is the source of energy for muscle contraction, maintenance of ion gradients, electrical conductance, biosynthesis of new molecules, and degradation of organic compounds [9].

The concept of energy balance is based on the first law of thermodynamics: energy is conserved [10].

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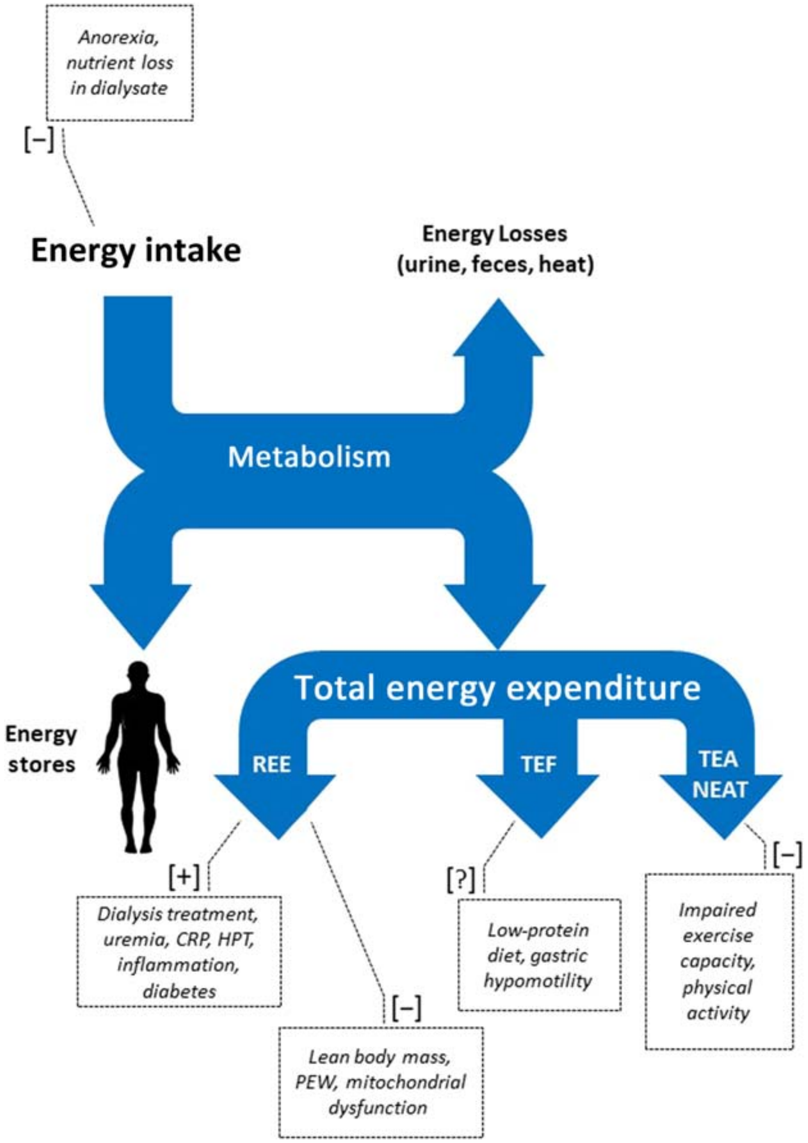
Anorexia, nutrient loss in dialysate
[−]
Energy intake
Energy Losses (urine, feces, heat)
Metabolism
Energy stores
Total energy expenditure
REE
TEF
TEA NEAT
[+]
Dialysis treatment, uremia, CRP, HPT, inflammation, diabetes
[−]
Lean body mass, PEW, mitochondrial dysfunction
[?]
Low-protein diet, gastric hypomotility
[−]
Impaired exercise capacity, physical activity

FIGURE 5.1 Principles of energy balance and components affected by CKD. *CKD*, Chronic kidney disease.

Energy balance is the difference between energy intake and energy output. Energy intake consists of the metabolizable energy of the foods consumed, and energy output represents the total energy expended [11]. Conservation of energy implies that the chemical energy stored in food is converted into work, thermal energy, and/or stored as chemical energy in fatty tissue. If energy intake is greater than energy output, a person is in positive balance and is storing energy as fat, carbohydrate, and protein. If energy output is greater than energy intake, a person is in negative balance and must be oxidizing endogenous stores of energy [9].

When humans ingest carbohydrates, proteins, or fats, they either oxidize them immediately and use the energy released to do work or transform them into forms that can be stored as potential energy [9]. The body stores energy as fat, glycogen, and protein. Differences in the metabolizable energy of dietary fat and carbohydrate mean that an increase in the quantity of fat in the diet is more critical than a comparable increase in carbohydrate when determining whether stores of triglycerides in adipose tissue will be increased [12].

When exogenous energy is not available, as occurs during an overnight fast, the body derives energy from its endogenous fuels [9]. Most of the energy stored in the body is as fat. A normal 70-kg man has about 13 kg of fat, which can yield approximately 125,000 kcal (525,000 kJ) on oxidation. Body protein is also lost during a total fast [7,13]. A normal man has about 11 kg of protein of which 7 kg are intracellular and 4 kg extracellular. The extracellular or structural proteins in bone and connective tissue are very stable and are considered to largely be unavailable for metabolic needs. The intracellular proteins, which make up much of the body's active cell mass, serve many functions but are chiefly enzymes and contractile proteins; there are no storage proteins. Due to the essential functions of protein, loss of large amounts of body protein may lead to adverse functional consequences that are conventionally considered to be the cause of death in long-term starvation [14,15]. Finally, the body contains between 1000 and 3000 kcal of carbohydrates stored in the liver and muscles as glycogen. This energy source is available for immediate energy needs, such as exercise, but is of little value during long-term fasting by virtue of its limited supply.

Suboptimal nutritional status in the form of protein-energy wasting (PEW) and overweight/obesity are the most frequent nutritional imbalances observed in CKD. PEW is defined as abnormally low levels or excessive losses of body protein mass and energy reserves [16]. Worldwide, the prevalence of PEW in CKD (stages 3–5) ranges from 18% to 80% [16–18]. Overweight/obesity and diabetes mellitus are some of the leading causes of CKD [19]. Around 20%–60% of CKD patients (stages 3–5) have a body mass index (BMI) greater than 25 kg/m^2 and almost half of the individuals with CKD also have diabetes and self-reported cardiovascular disease [20]. The causes of PEW and overweight/obesity in CKD are multifactorial and center around the common theme of energy imbalance [21]. As shown in Fig. 5.1, all the components of the energy balance equation have the potential to be altered because of CKD.

Energy intake

The fundamental basis for measuring energy intake is that in weight-stable individuals, energy intake is equal to total energy expenditure (TEE) [22–26]. Both prospective and retrospective methods have been used to assess dietary intake at the individual level, including food records, 24-hour recalls, and food-frequency questionnaires (FFQs). The gold standard for assessing the validity of dietary intake instruments is to compare the reported intake to the doubly labeled water (DLW) measures of energy expenditure [22]. The food record is an example of a prospective, quantitative method in which the participant records all foods and beverages and the amount of each consumed on a daily basis. The food record is usually collected over a 3- to 14-day period [22,23]. The strength of the food record method is its ability to capture quantitative information because all foods and beverages are weighed or measured before consumption. However, food records are subject to systematic errors such as underreporting, especially by certain populations (such as obese individuals or chronic dialysis patients) and their potential to influence and alter eating habits during data collection, which reduces the accuracy of usual intake estimates [24].

Retrospective dietary assessment instruments rely on the memory of the participant to recall foods or beverages consumed in the past; they include the 24-hour recall, diet history, and FFQ [22,23]. A 24-hour recall requires the respondent to recall in detail the foods and beverages consumed during the previous 24 hours. Data can be collected over a single 24-hour period or averaged from multiple 24-hour recalls conducted on both weekdays and weekend days. Although this method is quick and inexpensive, it has major limitations of rarely representing an individual's typical intake, it relies on memory, and often foods are omitted leading to low estimates of energy intake [23]. Finally, the FFQ requires that respondents report the frequency of consumption of foods from a list of foods over a specific time period. A strength of the FFQ is its easy and simple administration and ability to capture the intake of infrequently consumed foods [22,25]. However, FFQs are thought to have low precision at the individual level, are only semiquantitative, and are subject to misreporting errors [24].

In CKD, it is critical to accurately measure energy intake as part of an overall assessment of clinical and nutritional status, especially in the absence of the ability to directly measure TEE. Reduced energy and/or protein intake, associated with loss of appetite, has been associated with a decline in nutritional status, characterized by changes in serum albumin and increased risk of morbidity and mortality in patients with advanced CKD [2,3]. In fact, the prevalence of appetite loss among advanced CKD patients is reported to be 35%–50% [27,28]. As kidney function declines, food intake decreases, and this decrease correlates with the accumulation of nitrogen-derived uremic toxins [16,29]. In stable appearing maintenance hemodialysis (MHD) patients, fair or poor appetite can be associated with serological evidence for inflammation and increased mortality [30]. Abnormalities of the digestive system are additional factors beyond metabolic disturbances that may affect food intake [2]. Certainly, for CKD patients, inadequate dietary intake has been identified as the most frequent cause of PEW [27]. PEW is a manifestation of a progressive anorexia, which results from increases in anorexigenic hormones [31] and activation of proinflammatory cytokines, all of which lead to inadequate dietary protein and energy intakes. In a cross-sectional study, Kopple et al. [29] reported that in CKD patients, dietary protein and energy intakes, as well as serum and anthropometric measures of protein-energy status, progressively declined as estimated glomerular filtration rates (GFRs) decreased. In fact, the probability of PEW is inversely related to estimated GFRs [32]. As a result, PEW is more common in the more advanced stages of CKD.

Among clinically stable CKD patients, a contradiction exists between the observation of a stable body mass despite reported insufficient energy intakes [33–35]. This discrepancy may be due to underreporting of energy intake due to the poor accuracy of dietary assessment tools; this underreporting may affect the interpretation of health and diet studies [26] which can potentially lead to erroneous energy recommendations. Published data demonstrate an underreporting of dietary energy intake in nondialyzed advanced CKD patients [36,37], as well as in those undergoing MHD [33,34,38,39] and peritoneal dialysis (PD) [18]. The prevalence of underreporting is significant and has been observed in 72.5% of nondialyzed CKD patients [36,37], 52.5% of PD patients [18], and 77%–92% of MHD patients [33]. It is interesting to note that underreporters tend to have a high BMI when compared to valid reporters [18,36,37], an association that is routinely seen in individuals without CKD. Nevertheless, with proper training and extended recording periods (7 days), food records can provide accurate information about energy intake in CKD [40,41]. Furthermore, the reliability of these various tools and therefore the correct interpretation of data extracted from them is facilitated by integrating the dietary intake data into an overall picture of the patient's nutritional status, including weight change, level of physical activity, metabolic stressors, and treatment goals.

The 2019 Clinical Practice Guidelines on Nutrition in CKD [6] considers dietary intake data essential for the nutritional management of CKD patients and recommends the use of a 3-day food record, which includes both dialysis and nondialysis treatment days, as the preferred method to assess dietary intake in adults with CKD stages 3–5D. Twenty-four-hour food recalls and FFQs are considered alternative methods to assess dietary energy intake. The guidelines also recommend that to effectively plan nutrition interventions, factors beyond dietary intake must be taken into consideration (i.e., the patient's medication, knowledge, beliefs, attitudes, behavior, access to food, depression, and cognitive function).

Energy expenditure

An individual's energy requirements are the energy intakes that will balance TEE. Energy is expended by the body in the form of basal energy expenditure (BEE), resting energy expenditure (REE), the thermic effect of food (TEF), and physical activity thermogenesis or the work derived from all forms of physical activity, postural maintenance, and muscular contraction {exercise [thermic effect of activity (TEA)] and nonexercise activity [nonexercise activity thermogenesis (NEAT)]} [9,42]. These components make up a person's total daily energy expenditure. Regulation of energy balance is based on a complex set of feedback mechanisms that involve the endocrine system, central nervous system, and body energy stores and are aimed at restoring balance and maintaining body weight or, more precisely, body energy stores [1,12]. The main determinants of energy balance and the regulatory mechanisms of energy homeostasis in CKD are affected by both the underlying disease processes and the treatments for the disease (i.e., renal replacement therapy) [1,28]. In addition to the standard determinants of energy expenditure (age, sex, and fat-free mass, FFM), patients with CKD on MHD or PD often experience hyperparathyroidism (HPT), hyperglycemia, and chronic inflammation, which must be considered when assessing energy needs. As with any individual, illness, injury, and nutritional status goals (weight maintenance, loss, or repletion) are also factors that determine energy needs. Finally, the stage of CKD and the mode of renal replacement therapy are factors that have the potential to influence energy intake, energy expenditure, and, therefore, overall energy needs.

Basal energy expenditure and resting energy expenditure

BEE is the minimum amount of energy expended that is compatible with life. BEE typically represents 60%–70% of TEE. The REE is the amount of energy expended by a resting individual in a thermoneutral environment without the effects of meal consumption, physical activity, or physiological or mental stress [9,13,43,44]. REE may be 10%–20% greater than the true basal metabolic rate. REE also differs from BEE; in that, it is measured in the morning upon awakening after 12–18 hours of rest and is dependent on the circadian rhythms at that time of day [13,43,45,46]. The energy expended at rest includes the costs of maintaining the biochemical and structural integrity of the body; performing internal work, ion pumps, synthesis, and degradation of cell constituents; biochemical cycles; and leakage of protons across the mitochondrial membrane [9]. The effects of CKD on REE are described in the "Energy balance and chronic kidney disease" section.

Thermic effect of food

The TEF is manifested as the increase in energy expenditure immediately following meal ingestion [45,47]. It is also referred to as diet-induced thermogenesis and the specific dynamic action. The primary determinants of TEF are the nutrient composition and energy content of the food consumed [45,48]. All TEF studies agree that protein induces the greatest increase in the metabolic rate [48,49], followed by a mixed nutrient meal, carbohydrates, and then fat [49,50]. The second determinant of the magnitude of the TEF is the energy content of the meal. It is well established that the magnitude of the TEF is closely correlated to the energy load provided in a test meal [51].

The effects of CKD on TEF do not appear to have been evaluated. However, several factors common to CKD may affect the contribution that TEF has to TEE. First, gastrointestinal symptoms are common in patients with CKD and can be related to gastric hypomotility [52]. One way in which the TEF might be affected is due to the load of the meal being spread out over a greater time frame. Furthermore, uremia, as well as dietary restrictions and pharmacotherapy, may alter the gut microbiome [52]. Alterations in the gut microbiome have been implicated in energy regulation, although not specifically related to TEF. Finally, patients with advanced CKD often consume a low-protein diet. Since protein has the highest TEF, a low-protein diet would likely decrease the TEF portion of TEE. To the authors' knowledge, the effect that these factors may have on TEF and energy balance has not been examined in CKD patients or experimental models of CKD.

Thermic effect of activity

Physical activity is defined as any bodily movement produced by skeletal muscles, which results in energy expenditure. The TEA is the energy expended above the resting level, both during and after physical activity. Activity thermogenesis can be conceptually divided into purposeful or intentional activity (exercise) and NEAT. For sedentary individuals, purposeful sporting exercise is minimal and so their exercise-related activity thermogenesis is zero; for those who do exercise regularly, exercise-related energy expenditure is generally 15%–30% of the total daily energy expenditure [12,43,44,53]. The contribution of exercise to TEE depends on the intensity of the work performed and the duration of the sum of all activities over the day. The variability of this component means that the rate of energy expenditure can be as low as 1.5 times the REE for clerical work or as high as 15 times the REE for running.

NEAT or the energy expenditure of spontaneous physical activity includes the combined energy costs of the physical activities of daily living, fidgeting, spontaneous muscle contraction, and maintaining posture when not recumbent and accounts for the remainder of the total daily energy expenditure for most individuals [42]. Occupation and leisure time are the two major predictors of NEAT and can range from 15% to more than 50% of an individual's total daily energy expenditure [42]

In CKD patients, nutrition and physical activity are closely associated [54]. Inadequate energy intake impairs physical performance, which favors a sedentary lifestyle and contributes to loss of muscle strength and mass [54]. In fact, it is well documented that physical activity is diminished in CKD especially in those undergoing dialysis treatment, although the contribution of low dietary energy intake to reduced daily physical activity of chronic dialysis patients has not been examined [55–57]. Impaired exercise capacity has even been described in nondialyzed CKD patients [58] who are reported to have lower median peak oxygen consumption levels, which can limit exercise capacity to the extent that activities of daily living are impaired [56]. Increased risk for mortality, possibly related in part to the increase in inflammatory markers that occur in association with loss of muscle mass [54–58], has also been associated with physical impairment in CKD (stages 2–4) [59]. Mafra et al. [35] reported that inflammation had a negative effect on TEA, a positive effect on REE, with an overall negative net effect on TEE. They concluded that patients with inflammation were less active and, consequently, their TEE was lower as compared with patients without inflammation. This decrease in activity-related thermogenesis may be a component of adaptation to the disturbances in energy homeostasis frequently observed in CKD. The contribution of exercise and physical activity to TEE is not fully understood and is identified as a future research priority in the 2019 Clinical Practice Guideline on Nutrition in CKD [6].

Factors that influence energy expenditure

Since 1915, when Benedict suggested that the "active body mass" determines the REE, it has been recognized that the amount of FFM in the body (body mass minus total fat mass) is highly predictive of the REE [7,43,60,61]. About 50%–80% of the variance between people in their REE can be accounted for by their FFM [7,43]. Even though REE and FFM are strongly correlated, the correlation is not linear in normal weight individuals, probably because of the varying compositions of the FFM at different total FFMs [43,60,61]. Anatomically as well as metabolically, FFM is heterogeneous. It consists of organs with a high metabolic rate and it also comprises skeletal muscle and bone mass with relatively low metabolic rates. Elia [62,63] highlighted the existence of large between-organ differences in the specific resting metabolic rate (K_i; metabolic rate for individual organs and tissues under resting conditions) values for seven organs and tissues in young adults with normal body weight, including 200 for liver, 240 for brain, 440 for heart and kidneys, 13 for skeletal muscle, 4.5 for adipose tissue, and 12 for residual mass (all units are in kcal/kg/day). Residual mass includes skeleton, blood, skin, gastrointestinal tract, lung, spleen, and other organs and tissues present in small amounts. According to Wang et al. [64], under resting conditions, heart and kidneys have the highest metabolic rates, twice those for liver and brain, as seen in Fig. 5.2. After the heart, the kidney has the second highest mitochondrial content and oxygen consumption [65]. The high resting metabolic rate for the kidney is related to the requirement for a high mitochondrial content to provide sufficient energy for tasks that are driven by ion gradients generated from Na^+-K^+-ATPase, such as nutrient reabsorption, blood pressure regulation, and maintenance of acid–base homeostasis [66]. However, the mechanism by which mitochondrial dysfunction contributes to energy balance in CKD is unclear.

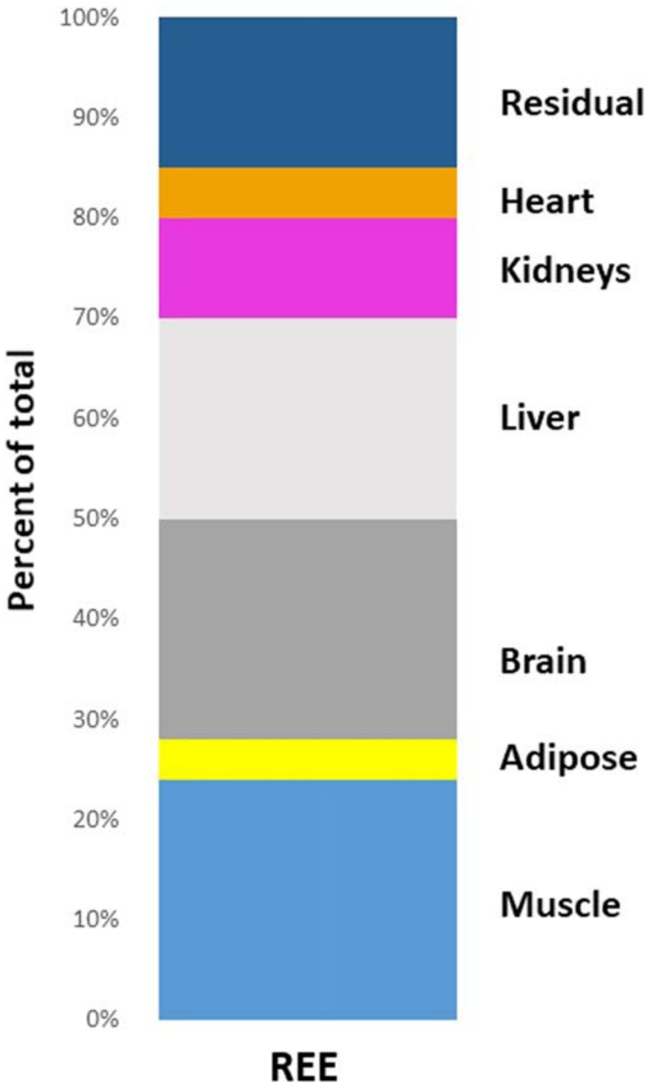

FIGURE 5.2 Proportional contribution of organs and tissues to calculated REE. *REE*, Resting energy expenditure.

Thyroid hormones (THs) play an important role in the regulation of energy expenditure. However, it is not known which of the triiodothyronine (T3) sensitive processes are most physiologically relevant for energy expenditure [67]. Numerous studies performed over the past century have demonstrated that TH helps to regulate energy expenditure in man. Administration of T3 to obese patients increases oxygen consumption even when these patients ingest an energy-restricted diet [68]. Thyroidectomy is followed by a significant (40%) decrease in BEE [69]. In a study of patients requiring chronic TH replacement, there was a significant negative correlation between REE and thyroid-stimulating hormone (TSH) [70]. THs are also important components of the metabolic adaptations associated with energy restriction and overfeeding [68]. THs directly and indirectly modulate the behavior of many metabolic pathways potentially relevant for energy expenditure. The direct effects refer to TH actions that increase ATP utilization related to metabolic cycles and ion leaks, while the indirect effects increase the capacity for energy expenditure through nongenomic pathways and mitochondrial biogenesis, as well as a decrease in metabolic efficiency at the stage of ATP production, by activating uncoupling mechanisms [67–70].

With respect to the kidney, TH directly influences renal growth and development, GFR, renal transport systems, and sodium and water homeostasis [71]. The thyroid–kidney mechanistic link has not been fully described but is thought to be bidirectional [72]. Studies have consistently shown that hypothyroidism and subclinical hypothyroidism are highly prevalent in the CKD population [73–75]. In addition, various thyroid functional test abnormalities are frequently seen in CKD patients, resulting from alterations in TH synthesis, metabolism, and regulation [73]. CKD is also known to be the cause of nonthyroidal illness [76], characterized by low T3 syndrome in the absence of underlying intrinsic thyroid disorder. With respect to renal replacement therapy, lower T3 and T4 values, higher TSH levels, higher frequency of low T3 syndrome, and subclinical hypothyroidism are more frequently observed in MHD patients as compared with healthy subjects [77]. Similarly, primary hypothyroidism, especially subclinical hypothyroidism, is not uncommonly encountered in PD patients [78,79]. Finally, studies have reported that the most common thyroid imbalance in renal transplant recipients is a low T3 syndrome with free T3 levels in the normal range [80,81]. The role that these disturbances in thyroid function have on energy metabolism in CKD patients has not been specifically evaluated. However, it has been suggested that low serum-free T3 levels in uremia may be the result of an appropriate adaptive process aimed at reducing energy expenditure and minimizing protein catabolism [82,83].

Measurement of energy expenditure

The variability of measured energy intake between individuals is greater than that of energy expenditure. Theoretically, energy requirements can be estimated by monitoring chronic dietary intake in people who are not gaining or losing weight. However, this is deceptively difficult to do because when dietary energy intake is measured, food and energy intake often change [11]. This suggests that energy requirements can be estimated more accurately from energy expenditure than from energy intake measurements [11]. Energy expenditure can be assessed by two different techniques: those that are calorimetric in nature (direct and indirect calorimetry) and that are noncalorimetric (DLW and energy intake) [11,43,44,84].

Direct calorimetry

The direct method for measuring metabolic rate involves the measurement of heat losses. Direct calorimetry measures the sum of radiant heat exchange and of convective, conductive, and evaporative heat transfer [43,44]. The total heat loss is equal to the rate of energy utilization when body temperature is constant [10,85,86].

Direct calorimetry has the advantage of being based solely on the direct measurement of heat generation and not on any assumptions about the physiology of energy metabolism, but it requires expensive instrumentation. The subject is placed in a thermically isolated chamber and the heat he/she dissipates is collected and measured [85]. This method is limited by the confining nature of the testing environment. Furthermore, direct calorimetry cannot be used to measure the short-term effects of thermogenic stimuli, such as food, on heat exchange due to the large heat storage capacity of the body [7,85]. It is also very costly. As a result, direct calorimetry is infrequently used.

Indirect calorimetry

Indirect calorimetry is the method by which metabolic rate is estimated from measurements of oxygen consumption and carbon dioxide production and is based on a series of assumptions and equations [43,85–88]. Indirect calorimeters can measure energy expenditure in both mechanically ventilated and spontaneously breathing patients. The measurement is based on the assumption that all the O_2 consumed (VO_2) is used to oxidize degradable fuels and all the CO_2 produced in the body (VCO_2) is recovered [9]. Calculating energy production in this situation is equivalent to converting the chemical-free energy of nutrients into the chemical energy of ATP plus loss of some energy (as heat) during the oxidation process, plus the ultimate conversion of the chemical energy to heat lost to the environment (plus any external work performed on the environment). Eventually, all energy is converted into heat so direct and indirect calorimetry should and do provide identical rates of energy expenditure under steady-state conditions [86]. The accuracy of respiratory gas exchange as an indicator of energy expenditure has been reported to be accurate to within 2% [10].

The 2019 Clinical Practice Guidelines on Nutrition in CKD [6] recommends that indirect calorimetry to measure REE is used to assess energy requirements when feasible and indicated in adults with CKD stages 1–5D and posttransplant. This recommendation represents a shift to a more personalized, patient-centered approach; however, the practicality of measuring rather than estimating REE makes it unlikely to be widely applied in the clinical setting at this time.

Doubly labeled water

The DLW method is based on the observation that the oxygen in respiratory carbon dioxide is in isotopic exchange equilibrium with the oxygen in body water [44]. The basis of DLW is that two isotopes of water ($H_2{}^{18}O$ and ^2H_2O) are given and their disappearance rates from the body (from body fluid such as urine) are monitored for a period of time optimally equivalent to 1–3 half-lives for isotope disappearance (7–21 days in most human subjects) [89]. The disappearance rate of ^2H_2O reflects water flux, while that of $H_2{}^{18}O$ reflects water flux plus carbon dioxide production rate. The difference between the two disappearance rates can be used to quantify the carbon dioxide production rate. To predict TEE from a measurement of carbon dioxide production, the respiratory quotient of the subject during the measurement period must be estimated [90]. The DLW method has been validated by comparing DLW-derived estimates of TEE with measurements made in a whole-body calorimeter [89,91]. While this technique for assessing energy expenditure appears highly reliable, it is not considered practical for outpatient clinical use. It also has limited use in CKD due to dialysis-induced shifts in body water, which can alter the isotopic abundance of the body.

Energy balance and chronic kidney disease

As illustrated in Fig. 5.1, CKD has the potential to affect many aspects of energy balance. The overall impact of CKD on energy balance can be both positive, with body weight (adipose tissue) gains, and negative, with fat loss. Many clinical disturbances and the treatments [92–94] associated with CKD have the potential to increase catabolism and elevate REE. Conversely, low energy intake can produce metabolic changes similar to those seen with adaptation to starvation, namely, reduced REE, body fat loss, and reduced physical activity [15]. Ku and coworkers [95,96] found that in both adults and children with CKD, weight/BMI declines significantly after eGFR falls below about 35 mL/min/1.73 m^2. Furthermore, they found a 55%–60% higher adjusted rate of death after starting either hemodialysis or PD in patients with a predialysis annualized weight loss greater than 5%. Although not measured, this weight loss presumably reflects decreased food and energy intake. The 2019 Clinical Practice Guidelines on Nutrition in CKD [6] underscores the importance of patterns of weight change since they can provide insights into the appropriate timing of nutritional interventions that might achieve the greatest impact on outcomes of patients with CKD [95,97,98]. The guidelines recommends monitoring body weight/BMI and body composition for changes at least monthly in MHD and PD patients, every 3 months in stages 4–5 and posttransplant patients and every 6 months in stages 1–3 patients [6].

One of the most common disturbances to energy balance today is the development of overweight/obesity. Obesity increases the risk for type 2 diabetes, cancer, hypertension, dyslipidemia, cardiovascular disease, sleep apnea, CKD, and chronic kidney failure [99]. The prevalence of obesity in patients with kidney failure is increasing faster than the prevalence of obesity in the general population [100], which suggests that obesity is a risk factor for CKD and its progression to kidney failure [101]. The prevalence of obesity among US patients awaiting a kidney transplant had also increased [100] and obesity has been identified as an independent risk factor for complications occurring during or after kidney transplant surgery including graft loss and patient death [102,103]. Weight management in CKD patients remains a controversial topic. On the one hand, weight loss in the predialysis phase may slow the progression of kidney disease [104]. On the other, obesity has been shown to confer a survival advantage in obese patients on dialysis and may reduce short-term mortality associated with malnutrition, inflammation, and PEW [5,104]. As a result of this obesity paradox, the appropriate weight management approach of overweight/obese predialysis and dialysis patients has not yet been established [101].

In general, studies report normal energy requirements in clinically stable CKD patients [92,94,105–111]. Most of the published data showed that REE of clinically stable chronic dialysis patients is normal in dialysis-dependent patients and below normal in nondialyzed CKD patients in comparison to the REE of healthy controls. Monteon et al. [39] were the first to examine the REE of nondialyzed CKD patients and MHD patients and showed that REE was not different from that of healthy controls. Similar findings have been reported in patients on both hemodialysis and PD [106,112]. In nondialyzed CKD patients, REE was reported to be about 100–200 kcal/day lower than that of healthy individuals in some studies [17,113] but not all [39]. Conversely, a study by Ikizler et al. [92] reported a significant 15%–20% increase in energy expenditure in MHD patients during dialysis sessions compared with control subjects. Although this data was characterized as REE, the patients had, in fact, eaten prior to the assessment of energy expenditure suggesting that some of this increase can be attributed to the TEF. The same patients had their REE measured on the interdialytic day after a 12-hour fast and were found to have a 7.5% increase in REE compared with control subjects. Finally, Shah and coworkers [114,115] concluded that the average daily energy requirements of MHD patients were similar to those of sedentary normal individuals, although there was wide variability among individual patients.

REE has been examined within PD cohorts with a wide array of comorbidities and varying degrees of residual renal function. Loss of residual renal function in PD patients has been shown to be associated with increased REE [116,117]. In fact, although several factors [diabetes, cardiovascular disease, C-reactive protein (CRP)] are positively associated with REE, residual renal function showed the strongest inverse relationship in this patient population. These data suggest that diseased kidneys likely remain a metabolically highly active organ and contribute to the REE of PD patients. It should be noted that increased uremia, inflammation, and secondary HPT also occur with the decline in renal function and may relate to the increased REE [118–121]. Stenvinkel et al. [121] showed that increased leptin levels in PD patients are associated with inflammation and loss of lean body mass. In the hypothalamus, leptin plays an important role in the regulation of energy homeostasis. In PD patients, it has been suggested that the net result of increased leptin is reduced intake and increased energy expenditure, which are known features of PEW [122].

The lack of consistent findings across the spectrum of CKD may be related to large variations in the degree of clinical disturbances that afflict CKD patients. This may be the reason that the reported energy requirements in stable CKD patients vary considerably [123]. It is likely that unless a chronic or severe condition is present, these disturbances will only have a modest effect on energy expenditure [1]. On the other hand, it has been clearly demonstrated that REE is increased with catabolic conditions often observed in patients with CKD, such as poorly controlled diabetes mellitus, severe HPT, and inflammation. Avesani et al. [109] showed that the REE in nondialysis CKD patients with poorly controlled diabetes was 12.5% greater than that of nondiabetic nondialyzed patients with CKD. Patients with severe HPT had significantly higher REE than patients with moderate HPT or healthy controls and 6 months after parathyroidectomy, the REE decreased significantly [108]. While the great majority of CKD stages 1, 2, and 3A patients do not have increased inflammatory markers, in some studies, 30%–50% of nondialyzed advanced CKD patients [111] and dialysis [124] patients present serologic evidence of an activated inflammatory response with elevated serum CRP. Avesani et al. [109] reported increased REE in nondialysis patients with CRP greater than 40.5 mg/dL. Finally, Utaka et al. [94] showed that after treatment of infection/inflammation, a significant decrease in CRP was accompanied by a 13% reduction of REE. Individualized, patient-centered assessment of energy requirements is clearly critical to effectively provide nutrition therapy in CKD.

The transition from kidney failure to kidney transplant is a metabolic challenge due to hormonal shifts, variations in energy expenditure, and the metabolic disturbances associated with immunosuppression therapies [125]. The hypercatabolic state that may be present with advanced CKD typically recovers in the first year after transplant [126]. In the early stages of postkidney transplant, surgical stress and increased doses of immunosuppressive drugs can lead to net protein catabolism and increased energy expenditure [127,128]. After successful transplantation with recovery of renal function, there is an improvement of nutritional status and oxidative stress, as well as a decrease in REE [128]. Ultimately, REE measured in transplanted patients [129] are similar to those estimated in healthy controls [130].

Predictive energy equations

In CKD, the preferred method to determine energy requirements is to measure REE using indirect calorimetry [131]. However, this approach is infrequently used in the clinical setting, because the method is both cumbersome and costly [132,133]. Table 5.1 lists the most commonly used predictive equations and recently developed disease-specific equations to estimate REE. The equations proposed by Mifflin and St Jeor in 1990 [109], Schofield in 1985 [134], and Harris and Benedict in 1919 [135] provide validated estimations of REE as compared with indirect calorimetry and are used routinely in healthy individuals [136]. Traditionally, these equations incorporate variables such as gender, age, height, and weight as predictors of measured REE. There has been limited

TABLE 5.1 Predictive energy equations.

Harris–Benedict RMR[a] [135]		
Men	$66.47 + 13.75 \times \text{weight} + 5.0 \times \text{height} - 6.75 \times \text{age}$	
Women	$655.09 + 9.56 \times \text{weight} + 1.84 \times \text{height} - 4.67 \times \text{age}$	
Mifflin–St Jeor RMR[a] [115]		
Men	$9.99 \times \text{weight} + 6.25 \times \text{height} - 4.92 \times \text{age} + 5$	
Women	$9.99 \times \text{weight} + 6.25 \times \text{height} - 4.92 \times \text{age} - 161$	
Schofield RMR[b] [134]		
	Men	Women
18–30 years	$15.3 \times \text{weight} + 679$	$14.7 \times \text{weight} + 496$
31–60 years	$11.6 \times \text{weight} + 879$	$8.7 \times \text{weight} + 829$
>60 years	$13.5 \times \text{weight} + 487$	$10.5 \times \text{weight} + 596$
Vilar REE[c] [142]		
$\text{REE} = -2.497 \times \text{age} \times \text{Factor}_{\text{age}} + 0.011 \times \text{height}^{2.023} + 83.573 \times \text{weight}^{0.6291} + 68.171 \times \text{Factor}_{\text{sex}}$		
Byham-Gray REE[d] [143]		
Male REE	$1027.8 - (5.19 \times \text{age}) + (9.67 \times \text{weight}) + (2.71 \times \text{CRP})$	
Female REE	$820.47 - (5.19 \times \text{age}) + (9.67 \times \text{weight}) + (2.71 \times \text{CRP})$	

[a] *Healthy patients, weight in kilograms (kg) and height in centimeters (cm).*
[b] *Healthy patients, reported by the World Health Organization, height in meters (m).*
[c] *Dialysis patients, height (cm), weight (kg), age (years).* Factor_{age} *is 0 if age is <65 years or 1 if >65 years.* $\text{Factor}_{sex} = 0$ *if female or 1 if male.*
[d] *MHD patients, age (years), postdialysis weight (kg), and CRP (mg/dL).*
CRP, C-reactive protein; *MHD*, maintenance hemodialysis; *REE*, resting energy expenditure; *RMR*, resting metabolic rate.

success in extrapolating these predictive equations to CKD [35,137]. The Harris–Benedict equation has been shown to both overestimate REE across the different stages of CKD [138–141] and to underestimate REE in MHD [142]. The Schofield equation also is reported to both overestimate REE in nondialyzed, MHD and PD patients [138,139,142] and to underestimate REE in MHD patients [136]. Finally, the Mifflin–St Jeor equation is reported to underestimate REE in MHD patients [114].

More recently, CKD-specific equations that incorporate both demographic and clinical variables as predictors of REE have been proposed [142,143]. Byham-Gray et al. [143] incorporated CRP as a variable in their equation and had greater precision in estimating REE as compared to the Mifflin–St Jeor equation [115]. Vilar et al. [142] developed a dialysis-specific equation (MHD and PD) which used standard demographic variables as predictors of REE; they also concluded that their equation was better than traditional predictive equations for REE in MHD or PD patients. Consistent with these findings, the 2019 Clinical Practice Guidelines on Nutrition in CKD [6,144] recommends that if indirect calorimetry is not available, disease-specific predictive equations may be used to estimate REE in metabolically stable adults with CKD 5D on MHD. But this remains a needed area for further study as these equations have not been validated in large populations to the same extent as those developed for healthy populations.

Overview and recommended energy intake in chronic kidney disease patients

The World Health Organization defines energy requirements as "the amount of food energy needed to balance energy expenditure in order to maintain body size, body composition and a level of necessary and desirable physical activity consistent with long-term good health" [134]. They caution that dietary energy needs must be considered within the context of other nutrients in the diet since the lack of one will influence the others. There are several reasons why this is a consideration of critical importance in CKD: adequate energy intake is needed for effective utilization of dietary protein; protein-energy malnutrition is a common cause of PEW [118,145]; reduced dietary energy intake is common [146]; nondialyzed advanced CKD patients are often prescribed low-protein diets that may increase their risk of protein wasting when energy intake is marginal or insufficient; and PEW is associated with increased morbidity and mortality in these individuals [32,147].

Table 5.2 summarizes recommended energy intakes across the CKD spectrum. A consistent recommendation of 25–35 kcal/kg/day is based on the amount needed to maintain body protein stores and nitrogen balance and includes patients consuming the full range of dietary protein intakes. The recommendations are calculated based on desirable body weight rather than actual body weight. Ideal body weight (IBW) is typically used as a surrogate for desirable body weight because it is the weight associated with the lowest mortality in the general population for a given height, age, sex, and frame size based on the Metropolitan Life Insurance Height and Weight Tables.

In 2010 the Academy of Nutrition and Dietetics (Academy) and the National Kidney Foundation's KDOQI [148] put forth guidelines for patients with CKD and end-stage renal disease. In 2019 KDOQI, in collaboration with the Academy, updated its Clinical Practice Guideline on Nutrition in CKD [6]. These recommendations are consistent with previous guidelines and reflect the current literature:

Methods to assess energy requirements:

- Adults with CKD 1–5D and posttransplant: use indirect calorimetry to measure REE when feasible and indicated.

TABLE 5.2 Recommended energy intake in adults, according to chronic kidney disease (CKD) stage.

CKD stage	Energy (kcal/kg/day)
Increased CKD risk with normal kidney function[a]	30–35; adjust for weight reduction (IBW) if BMI >30
Mild, moderate, advanced CKD[b]	30–35; increase proportion of LPD
Transition to dialysis	30–35
Dialysis dependent or any stage with PEW (existing or imminent)	30–35; higher intake if PEW present or imminent
Kidney transplant[a]	30–35
CKD and overweight/obese[a,c]	<30

[a] *In obese patients, lower energy ranges used based on IBW for weight reduction [5,6].*

[b] *LPD for management of CKD [5].*

[c] *In overweight/obese patients, diet to significantly reduce BMI [6].*

BMI, Body mass index; *CKD*, chronic kidney disease; *IBW*, ideal body weight; *LPD*, low-protein diet; *PEW*, protein-energy wasting.

- Adults with CKD 5D on MHD who are metabolically stable, in the absence of indirect calorimetry, disease-specific predictive energy equations may be used to estimate REE as they include factors that may influence the metabolic rate in this population.

Methods to assess protein and calorie intake:

- Adults with CKD 3−5D, use a 3-day food record, conducted during both dialysis and nondialysis treatment days (when applicable), as a preferred method to assess dietary intake.
- Adults with CKD 3-5 nondialyzed and 5D: 24-hour food recalls, FFQs, and normalized protein catabolic rate/normalized protein nitrogen appearance may be considered as alternative methods of assessing dietary energy and protein intake.

Recommended energy intake:

- Adults with CKD 1−5D and posttransplant who are metabolically stable: prescribe an energy intake of 25−35 kcal/kg IBW per day based on age, gender, level of physical activity, body composition, weight status goals, CKD stage, and concurrent illness or presence of inflammation to maintain normal nutritional status.

Abbreviations

ATP	adenosine triphosphate
BEE	basal energy expenditure
BMI	body mass index
CKD	chronic kidney disease
CRP	C-reactive protein
FFM	fat-free mass
FFQ	food-frequency questionnaire
HPT	hyperparathyroidism
IBW	ideal body weight
KDOQI	Kidney Disease Outcomes Quality Initiative
MHD	maintenance hemodialysis
NEAT	nonexercise activity thermogenesis
PD	peritoneal dialysis
PEW	protein-energy wasting
REE	resting energy expenditure
TEA	thermic effect of activity
TEE	total energy expenditure
TEF	thermic effect of food
TH	thyroid hormone

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CHAPTER

6

Uremic toxins: an integrated overview of classification and pathobiology

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Introduction

Uremia is conventionally defined as a condition due to an advanced insufficiency of the excretory function of the kidney (often called kidney failure) associated with the retention of urea and other products of cellular metabolism in blood and tissues. It is often accompanied by a diverse array of symptoms and signs affecting many organs and systems, called the *uremic syndrome. Azotemia* is a milder form of uremia, identified by an elevation of urea and other nitrogenous waste products in blood, that is not uncommonly asymptomatic.

As the overall function of the kidney declines in the course of chronic kidney disease (CKD), a wide variety of solutes derived from diet and endogenous metabolism that are normally dependent on glomerular filtration, tubular secretion or renal metabolism for elimination gradually accumulate in the body-fluid compartments [1–3]. Additionally, CKD is accompanied by a complex array of hormonal disturbances that lead to surfeits or deficiency in important biologically active molecules that can have marked effects on extrarenal organ function, such as bone, myocardium, nerves, and bone marrow. As pointed out by Zoccali and colleagues [3], CKD is a complex systemic disease, only partly explained by the accumulation of "uremic toxins." To better understand CKD an integrated systems biology approach is needed, incorporating such elements as energy balance, innate immunity, and neuroendocrine signaling, which collectively generate a phenotype affecting many organs and systems.

In sum, retained or endogenously generated solutes have diverse biological effects that result in the malfunction of various subcellular organelles, cell types, and organ systems. When these biological effects are sufficient to evoke clinically recognizable disturbances, the uremic syndrome (see Table 6.1) can be manifest and the offending molecules are collectively designated "uremic toxins" or "uremic solutes." [1–3]. These uremic toxins exhibit a broad array of physicochemical characteristics and have systematically been investigated for many decades leading to an extensive catalog of potential compounds and molecular entities [1–3] (see Table 6.2).

A complete characterization of the catalog of uremic toxins has great utility in the design of approaches for their removal by dialysis; for ways to enhance their removal by nondialytic methods; for creation of interventions to prevent/mitigate their formation or to enhance their nonrenal disposal; and for synthesis of inhibitors of their adverse effects on cells for organ systems—all directed at subjects with advancing CKD or kidney failure. The analysis of the issues surrounding uremic toxicity requires a useful definition and synthesis of a classification of uremic toxins. This essay attempts to provide a succinct and update approach to classification of uremic toxins and to provide and integrated overview of their pathobiology [1].

Definition of a uremic toxin

More than 4 decades ago, the late Jonas Bergstrom gave a definition of the uremic syndrome that is just a valid today as it was then [4]. He stated that the uremic syndrome is a "toxic syndrome caused by severe glomerular deficiency associated with disturbances in tubular and endocrine functions of the kidney. It is

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TABLE 6.1 Symptoms and signs of uremic toxicity (components of the uremic syndrome).

- Anorexia
- Nausea (especially in early morning)
- Vomiting
- Dysgeusia
- Uremic fetor
- Stomatitis
- Diarrhea
- Pruritis
- Urochrome pigmentation
- Uremic "frost"
- Onychodystrophy ("half and half" nails)
- Pallor (anemia)
- Vascular calcification ("ossification")
- Periarticular calcium deposits
- Calciphylaxis
- Weakness
- Easy fatigability
- Protein-energy wasting
- Peripheral neuropathy—paresthesia (numbness/tingling in limbs)
- Carpal tunnel syndrome (β_2-microglobulin amyloidosis)
- Impotence
- Shortness of breath (anemia, uremic pulmonary edema, and pleural effusions)
- Chest pain (pericarditis/pleuritis)
- Easy bruising/bleeding gums
- Joint pain (gout and pseudogout)
- Joint destruction (β_2-microglobulin amyloidosis)
- Impaired cognition
- Sleep disturbances
- Drowsiness
- Seizures
- Coma

TABLE 6.2 A catalog of the major organic uremic toxins.

Low molecular weight, polar (water soluble)

- Guanidines (ADMA, GAA, GSA)
- Oxalates
- Phenylacetylglutamate
- Methylamine (TMA N-oxide)
- Sulfuric compounds
- Myoinositol
- 2PY
- Polyamines (putrescine, spermine)
- Urea (isocyanate)
- Carbamylated compounds
- Ammonia
- Uric acid
- Xanthines

Protein bound, water soluble

- Advanced glycation end products
- Advanced oxidation protein products
- CMPF
- Cresols (*p*-cresyl sulfate)
- Hippurates
- Homocysteine
- Indoles (indoxyl sulfate, kynurenines)
- Phenols (phenylacetic acid)
- Quinolinic acid

Middle and higher molecular weight

- Adrenomedullin
- Adipokines (adiponectin. leptin)
- Atrial natriuretic peptide
- β_2-Microglobulin
- β-Endorphin
- β-Lipotropin
- Cholecystokinin
- Complement factor D or B
- Cystatin C
- Interleukins (1,6, 8, 10)
- Tumor necrosis factor
- Endothelins
- FGF-23
- Ghrelin
- Glomerulopressin
- Parathyroid hormone
- Peptide YY
- Prolactin
- Resistin
- Visfatin

ADMA, Asymmetric dimethylarginine; *CMPF*, 3-carboxy-4-methyl-5-propyl-2-furanproprionic acid; *FGF-23*, fibroblast growth factor-23; *GAA*, guanidine-acetic acid; *GSA*, guanidine-succinic acid.

Adapted from Vanholder R, Pletinck A, Schepers E, Glorieux G. Biochemical and clinical impact of organic uremic retention solutes: a comprehensive update. Toxins (Basel) 2018;10:pii. E33.

characterized by the retention of toxic metabolites, associated with changes in the volume and composition of the body fluids and an excess or deficiency of various hormones." This very inclusive definition allows the uremic syndrome to embrace the retention of solutes due to failure of renal excretion (glomerular and/or tubular insufficiency) and hormonal surfeits or deficiencies arising from the disturbances wrought by kidney disease itself.

From this analysis, it is clear that uremic toxins must be defined via a causative link between the putative toxic substance and one or more of the pathophysiological manifestations of the uremic syndrome. Making this connection requires that a series of criteria be fulfilled, called the Massry/Koch postulates—so-called because they are a derivative of Koch's postulates for defining a pathogenic organism, as developed by one of the coauthors of this essay (SGM), more than three decades ago [5]. These postulates establish the requirements for an "authentic" uremic toxin as follows:

1. The toxin must be identified and characterized as a unique chemical entity.
2. Quantitative analysis of the toxin in biological fluids must be possible.
3. The level of the putative toxin must be elevated in biological fluids of subjects with the uremic syndrome.

4. A relationship between the level of the putative toxin in biological fluids and one or more of the manifestations of the uremic syndrome must be present.
5. A reduction in the levels (or total body burden) of the putative toxin in biological fluids must result in some measurable amelioration of uremic manifestations.
6. Administration of the putative toxin to achieve levels similar to that observed in the uremic syndrome must reproduce the uremic manifestations in otherwise normal animals or man (in vitro demonstration of cellular toxicity alone is insufficient to meet this criterion).

A seventh criterion could be added to this list; that a consistent and plausible pathobiological mechanism should be able to explain the linkage between the putative toxin and the uremic manifestation (e.g., organelle dysfunction, inhibition of signal transduction, and metabolic perturbations). These postulates are difficult to apply directly to those disturbances that are part and parcel of the uremic syndrome but which emanate from deficiencies of certain hormones or biologically active peptides (e.g., erythropoietin, calcitriol) consequent to the loss of renal mass in CKD. Nevertheless, these postulates are quite useful for the definition of uremic toxins resulting from retention of solutes normally excreted by the kidney and substances that arise in enhanced levels endogenously (from excessive synthesis or impaired degradation) as kidney disease progresses to symptomatic uremia [e.g., parathyroid hormone (PTH)]. Obviously, diet per se is an important source of uremic solutes, but it is increasingly apparent that the intestinal microbiota play a very important role in endogenous generation of uremic solutes.

The demonstration of a causative linkage between a specific putative uremic toxin and a clinical manifestation of uremia can be a formidable task, as the symptoms and signs of "uremia" are extraordinarily diverse [6] (see Table 6.1), affecting many organs and systems. The ability of a specific putative toxin to elaborate a clinical manifestation is governed by a panoply of factors (see Table 6.3). These facts complicate enormously the task of identifying "authentic" uremic toxins as they require both longitudinal and cross-sectional analysis, body-fluid compartmental studies, and the influence of naturally occurring inhibitors and promoters. Some toxins may also exhibit "tropism" for specific cellular types or organ systems (e.g., neurotropism) (see next).

Classification of uremic toxins by physicochemical characteristics

An examination of putative uremic toxins according to their physicochemical characteristics (molecular mass, polarity, protein binding, and chemical structure) has been the time-honored and the most popular approach to their physicochemical classification [1–3]. In this schema, uremic toxins are categorized into four nonoverlapping categories: (1) polar, water soluble, nonprotein bound, and low molecular mass (<500 Da); (2) polar, water soluble, protein bound, and low molecular mass (<500 Da); (3) middle-molecular mass (>500 and <3000–12000 Da) and nonprotein bound; and (4) high-molecular mass (>3000–12,000 Da) and nonprotein bound [1–3]. The pioneering work of the European Uremic Toxin Work Group (EUTox) has been invaluable in creating a uniform approach to classifying uremic toxins and has pointed out the necessity for standardized schema for analysis of their in vitro effects and the enormous difficulties posed by variability in reported concentrations of putative toxins [2]. In their landmark initial review the EUTox group created an encyclopedic listing of uremic retention solutes (90 total), 68 of which were <500-Da molecular mass, 10 had a molecular mass of >500–12,000 Da, and 12 had a molecule mass of >12,000 Da. A total of 25 of the retention solutes were protein bound; all but 2 of these had a molecular mass of <500 Da. The concentration of these putative toxins in biological fluids ranged broadly from ng/L to g/L. Of all the toxins identified, almost 40% were either "middle" molecules or protein bound. Larger molecular-weight compounds (molecular weight between 16 and 60 kDa) represent a major challenge as many dialytic procedures are quite inefficient for their removal [7,8]. The "middle molecule" hypothesis of Babb and Scribner rests on the notion that molecules of 500–2000 Da can be responsible for the signs and symptoms of uremic

TABLE 6.3 Factors determining the toxicity of substances accumulating in uremia.

- The time-related evolution of the levels of putative toxins in biological fluids, for example, time-averaged vs peak levels cellular penetration into sites of action (cytoplasm, endoplasmic reticulum, mitochondria, nucleus)
- Metabolism to more (or less) toxic compounds
- Distribution in body fluids (protein binding. lipophilicity, hydrophilicity)
- Presence of naturally occurring inhibitors or promoters
- Rates of metabolism of putative toxins

Adapted and updated from Glassock RJ. Uremic toxins: what are they? An integrated overview of pathobiology and classification. J Ren Nut 2008;18:2–6.

toxicity (such as peripheral neuropathy), and their removal by dialysis is an important consideration in dialytic therapy of kidney failure [9–11]. Peritoneal dialysis may have a better profile of removal of higher molecular-weight solutes or protein-bound solutes, but this may not necessarily translate to better outcomes for peritoneal dialysis compared to hemodialysis [12]. However, formal testing of the added value of assessing the serum concentration of a given protein-bound solute for improving the dialysis prescription is largely lacking [13]. Such testing is sorely needed, in the authors' opinion.

The development of large-scale, rapid capillary electrophoresis—mass spectrometry, proteomic, and metabolomic analysis of body fluids—has greatly enhanced the ability to identify and characterize potential uremic toxins [14–18] (see Table 6.2). This original compendium from 2003 has been updated by Duranton and coworkers in 2012 [19] and by Vanholder and coworkers in 2018 [20]. Collectively, these studies demonstrated "uremic solute" serum concentrations in subjects with CKD, with many claims based on single reports (i.e., not reduplicated). Overall, 52 of 88 uremic solutes studied were based on single reports. Among those solutes based on multiple reports (total $n = 27$), 26% were low molecular weight and water soluble; 26% were protein bound; and 48% were middle or higher molecular weight. Importantly, some compounds defined as "uremic" solute had normal serum concentrations in patients with advanced kidney disease. A scoring system has been developed by Vanholder et al. [20] to categorize the strength of the association of the uremic solute to toxicity. The highest scores were found with three small water-soluble solutes [asymmetric dimethylarginine (ADMA), trimethylamine N-oxide (TMAO), and uric acid], six protein-bound solutes [AGEP, *p*-cresyl sulfate (pCS), indoxyl sulfate (IS), indole acetic acid, kynurenines, and phenylacetic acid], and three middle-molecular-weight compounds (β_2-microglobulin, ghrelin, and PTH). They concluded their extensive 2018 narrative review with a very telling statement:

> "the picture emanating is one of a complex disorder, where multiple factors contribute to a multisystem complication profile, so that it seems of not much use to pursue a decrease of concentration of a single compound [20]".

Inorganic substances (H_2O, Na^+, Cl^-, K^+, H^+, Mg^{++}, PO_4^-, Ca^{++}, and SO_4) and trace elements [e.g., Al, Cr, Se, Pb, Cu, and Cd (see next)] can also qualify as uremic toxins. For example, the retention of sodium chloride and water can evoke volume expansion and disastrous consequences on the cardiovascular system in CKD and end-stage renal disease (ESRD) and contribute markedly to organ dysfunction (left ventricular hypertrophy), morbidity (hypertension and congestive heart failure), and mortality (sudden cardiac death) (see also next) [21]. However, dietary salt excess and salt retention can also have many body fluid–independent effects on the vascular system, including fostering an inflammatory milieu [22,23]. Also, metabolic acidosis (retention of $H+$ ion) can wreak havoc in many cell and organ systems (such as bone and myocardium), and metabolic acidosis can itself perpetuate the progressive nature of CKD [24]. Divalent ions such as phosphate and calcium also participate in homeostatic disturbances associated with uremia [25]. These are discussed in more detail in Chapter 17, Disorders of Phosphorus Homeostasis: Emerging Targets for Slowing Progression of Chronic Kidney Disease, Chapter 23, Calcium, Phosphate, PTH, Vitamin D, and FGF-23 in CKD-Mineral and Bone Disorder, and Chapter 24, Phosphorus Metabolism and Fibroblast Growth Factor 23 in Chronic Kidney Disease. Trace elements (such as aluminum, lead, iron, selenium, strontium, silicon, copper, cadmium zinc, rubidium, molybdenum, and tin) have been studied for decades [26–30]. Although many of these elements can be increased in uremia, some are depleted (such as zinc and selenium) [29]. Some, such as aluminum, are increased in tissues and serum because of medication (aluminum-containing phosphate binders) or environmental exposure (contaminated water-cooking vessels) and can produce specific clinical abnormalities, such as aluminum intoxication, causing neurological abnormalities and aplastic bone disease [28]. Dialysis fluids can also serve as a source for an increased burden of trace metals [26].

Although many potential uremic toxins are elevated in plasma due to impairment of renal excretion, many are also associated with increased synthesis or impaired degradation of normal substances produced endogenously [e.g., PTH, and fibroblast growth factor-23 (FGF-23)]. It must be emphasized that the plasma concentrations of putative uremic retention solutes are very poorly correlated with the prevailing level of estimated glomerular filtration rate (eGFR) [31–35], and the plasma levels of each specific solute may have a unique association with the level of eGFR [34]. These data point out the major limitations of eGFR as a predictor of uremic solute concentrations [33]. These observations also add emphasis to a neglected phenomenon well-recognized in the aglomerular kidney of marine teleosts (i.e., anglerfish) [31], specifically that the tubules represent an important site for the elimination of putative toxic by-products of metabolism. This phenomenon was pointed out in an elegant essay by Jerome Lowenstein in 2011 [31].

Thus residual activity of transport systems in tubules of diseased kidneys [most specifically the organic anion transporters (OAT) in the proximal tubule] may have an important influence on the concentration of toxins at low levels of GFR [33–35]. This phenomenon gives rise to the notion that enhanced expression of the OAT might be able to limit the accumulation of uremic toxins even with advanced loss of GFR [1]. The kidney clearance of organic solutes secreted into the proximal tubule is strongly negatively associated with the degree of decline of eGFR in CKD [36]. Nevertheless, among pediatric patients undergoing maintenance hemodialysis (MHD) for ESRD, the serum levels of protein-bound solutes appear to be linked to the prevailing level of residual renal function and urine volume [33].

The low-molecular-mass solutes (<500 Da) have attracted a great deal of attention over many years. Urea (molecular weight 60 Da) is nonprotein-bound solute that has been used as a "surrogate" for "authentic" uremic toxins, although its intrinsic toxicity is greatly limited to very, very high plasma concentrations seldom achieved even in advanced uremia [37]. The evidence that urea per se functions as an authentic uremic toxin is very weak [37,38]. Nevertheless, its spontaneous degradation to isocyanate can lead to the carbamylation of serum and tissue proteins, such as albumin or hemoglobin, and amino acids. High urea concentrations in biological fluids can lead to insulin resistance, free radical production, cellular apoptosis, and disruption of the protective intestinal barrier—all linked to pathobiological changes seen with uremic toxicity [39]. Urea is an attractive "surrogate" marker of uremic toxicity as it is fundamentally derived from catabolism of dietary and endogenous somatic proteins. Urea is produced by the catabolism of endogenous or dietary proteins. In the intestine, it degrades to ammonia and CO_2 by the actions of bacterial urease. The ammonia can traverse to the liver, via the portal vein, and be reutilized for urea (or protein) synthesis by the liver. [40]. This extrarenal clearance of urea seems to be reduced in uremia [40], but due to the elevated plasma urea the formation of ammonia nitrogen from urea degradation is about the same in uremic and normal subjects (about 3.5 g/d) [40]. The administration of alpha-keto analogs of valine, leucine, isoleucine, methionine, and phenylalanine along with other essential amino acids can, at least in some uremic subjects, diminish the rate of urea appearance in plasma and body fluids perhaps by augmenting nitrogen conservation and reutilization or by promotion of net protein synthesis [41] (see also next).

The metabolism of amines, such as dimethylamine, trimethylamine, spermine, and putrescine, is disturbed in uremia and many amine compounds accumulate in plasma of uremic subjects [42], largely as a consequence of the actions of the intestinal microbiota. TMAO, an oxidation product of trimethylamine derived from choline, is synthesized by the intestinal microbiota metabolism of constituents of meat, including carnitine or lecithin, and may also be an important low-molecular-weight uremic toxin (see also next). The metabolism of phenylalanine and tyrosine is also disturbed in uremia, leading to increase plasma levels of phenylacetic acid, *p*-hydroxyphenylacetic acid, *p*-hydroxybenzoic acid, and phenylpyruvic acid in uremia [43].

Protein-bound uremic toxins are of great theoretical and practical importance [44–47]. Such protein binding may greatly limit the ability of diffusive or convective dialysis therapies to remove the compound efficiently, and this explains the limitations of extracorporeal therapies using membranes of low-molecular-mass "cutoff" for the treatment of uremia. Displacement of the uremic toxin from its protein-binding site (e.g., on albumin) might be a very attractive way of enhancing uremic solute removal by dialysis. For example, a recent study by Madero and coworkers has shown enhanced dialytic removal of protein-bound solutes by the infusion of ibuprofen (a competitive albumin binding inhibitor) into the arterial bloodline [48] (see also next).

The best studied of the protein-bound uremic solutes include pCS and IS [47,49,50]. Both of these uremic solutes originate in the colon from the action of resident bacteria—the intestinal microbiota on the amino acid tryptophan [51] Thus there is an important contribution of the colon to the uremic state [52–54]. Urea retention and other uremic solutes can lead to a dramatic alteration in the intestinal microbiota (the gut microbiome) [52–54]. The colon contains abundant nitrogenous compounds, many of which accumulate in the plasma of subjects with kidney failure and, therefore, qualify as potential uremic toxins [52,53]. Many of these are sulfated conjugates that are excreted normally by a combination of glomerular filtration and secretion by the proximal tubule [52,53]. Decreases in beneficial bacteria that provide nutrients to the intestinal epithelium are seen along with an increase in bacteria that synthesize damaging uremic toxins (such as pCS, IS, and TMAO) [54,55]. There is an important interaction of the enterohepatic cycle of bile acid metabolism and the gut microbial flora (reviewed in Ref. [56]) and these participate in the intestinal generation of uremic solutes. Local inflammation degrades the intestinal epithelial barrier function, and these toxic solutes are generally translocated from the intestinal lumen to the bloodstream, where they may have adverse effects on vascular calcification, cardiovascular function, atherogenesis, red blood cell generation, fibrosis, and immune dysfunction [57]. These phenomena provide a rationale for treatment of uremia by oral adsorbents [58], such as activated charcoal (AST-120; Kremezin) [58] or sevelamer [59] or by probiotics [60]. The oral absorbent Kremezin seems to have beneficial effects on lowering IS levels, but sevelamer has no substantial effect on either pCS or IS levels. Despite initially promising reports, Kremezin has inconsistent effects on CKD progression [58]. Interventional trials of the use of probiotics are still lacking [60]. Some studies have shown that pCS and IS promote vascular calcification and impair glucose tolerance in experimental animals [61]; however, in a large clinical trial of MHD patients (the HEMO study), a post hoc analysis suggested that neither pCS nor IS was associated with adverse cardiovascular outcomes [62]. In addition, recent studies have shown that hemodiafiltration is no better than hemodialysis for the removal of protein-bound uremic solutes [63] (see also next). Tryptophan-derived uremic solutes (such as IS) may have prothrombotic effects [64].

Other protein-bound uremic solutes include ADMA, homocysteine, nucleosides, and pentosidine. ADMA appears to accumulate in uremia more as a result of disturbed renal metabolism that from impaired renal excretion [65–68]. It is noteworthy that the R^2 value of ADMA levels in relationship to eGFR is only 0.167 (the R^2 value to creatinine is 0.737) [19,20]. Uric acid and other nucleotide derivatives are emerging as important candidates for low molecular mass uremic toxins [69,70]. Cellular mitochondria might serve as a source as well as a target of uremic toxins [71], thereby establishing a "vicious cycle" of positive feedback. Deoxyglucosone and advanced glycation end products may accumulate in uremia [1,2]. Thus several carbohydrate-derived moieties can contribute to the uremic state.

Middle molecules ($>500–12,000$ Da) have been regarded as important to the uremic syndrome and to the response of uremia to dialysis treatment ever since the seminal observations leading up to the "middle molecule hypothesis" were made by Babb and Scribner 45 years ago [72]. As noted earlier, EUTox identified about 10 such middle molecule uremic toxins in their initial survey [2,19,20]. These compounds are often glucuronide conjugates, polypeptides (such as β_2-microglobulin), carbohydrate derivatives, advance glycation or oxidation end products (AGEP/AGOP), or polypeptide hormones (such as parathyroid hormone (PTH) or its fragments, or fibroblast growth factor 23 (FGF-23)) [73,74].

β_2-Microglobulin (molecular weight 11.8 kDa) has attracted a great deal of attention. It is a constituent of the HLA (human leukocyte antigen) molecule located on the cell surface of all nucleated cells and is shed into the circulation at a relatively constant rate of about 50–200 mg/d, under normal noninflammatory conditions. The kidney is the major route of elimination for β_2-microglobulin so it accumulates in the plasma of patients with CKD and, because of its size, is poorly removed by standard dialysis [75–78]. Its toxic properties are due to the propensity to aggregate and form a misfolded protein with a β-pleated sheet (β_2-microglobulin amyloidosis) that preferentially deposits in large bones close to articular surfaces, synovial membranes, and carpal tunnel tissue, causing pain, bone destruction, malfunction, and disability. It is mainly seen in patients of late vintage hemodialysis (usually >8 years). The use of high-flux, biocompatible membranes can reduce the likelihood of these complications, via enhanced removal of β_2-microglobulin (see next). The incidence of β_2-microglobulin-related amyloidosis has been decreasing, probably because of wider use of biocompatible high-flux membranes, but prolonged survival of dialysis patients may offset this phenomenon [76–78].

PTH is the quintessential prototype of a high-molecular-weight uremic toxin. As stated earlier, it is one of only a very few uremic toxins that have fulfilled the Massry/Koch postulates. Intact (native) PTH has a molecular weight of 9.5 kDa, but in CKD both the intact hormone and metabolic fragments circulate. Elevated levels are virtually always seen in CKD, beginning at about Stage III. This is largely due to increased secretion caused by disordered homeostatic control (secondary hyperparathyroidism). The increased intact biologically active PTH (and its fragments) in CKD [79] can result in a plethora of manifestations, including osteitis fibrosis cystica (high-turnover bone disease) [80], impaired erythropoiesis (due to bone marrow fibrosis) [81], shortened red cell survival [82], cutaneous and subcutaneous calcific deposits [83], myocardial injury [84,85], leukocyte and immune cell dysfunction [86], impaired glucose homeostasis, and reduced insulin secretion [87] and defects in neuronal transmission [88] (reviewed in Ref. [89]). Many of these manifestations are linked to an increase in cytosolic calcium concentrations, but multiple mechanisms may contribute to these effects [90]. Lowering of serum PTH levels in uremia may prevent or ameliorate many of these uremic manifestations, particularly those involving bone (fractures, pain) and soft-tissue calcifications.

FGF-23 is another emerging candidate for a middle-molecular-weight uremic toxin [91–93]. It is a phosphaturic peptide hormone (molecular weight of 32 kDa) derived from the bone osteocyte that plays a central role in mineral metabolism by the regulation of renal phosphate handling, vitamin D metabolism, and PTH secretion (see earlier) [91–93]. Its function in the kidney depends upon a cofactor α Klotho, but it has many Klotho-independent extrarenal effects, especially on the myocardium [91–93], where it may induce myocardial hypertrophy. Serum levels of FGF-23 rise early in CKD and may have deleterious, Klotho-independent effects on myocardial function (uremic cardiomyopathy) and inflammation [91–93]. However, studies of FGF-23 in hemodialysis patients have challenged this hypothesis [94] (see also next).

The other high-molecular mass (> 12,000 Da) nondialyzable toxins have been less well characterized and include cytokines, chemokines, Ig light chains, complement factors, AGEP/AGOP, inhibitor proteins, and chemotaxis-inhibiting peptides [1,2] (see Table 6.2).

The pathobiologic categorization of uremic toxins according to the processes underlying accumulation in body fluids

Uremic toxins can accumulate in body-fluid compartments through a number of distinct mechanisms. A *Type I* mechanism represents the accumulation in body fluids of toxic substances normally produced *endogenously* by metabolic processes, including those that occur in intestinal microbiota, largely as a result of reduced renal excretory capacity (decreased GFR and/or tubular excretory function) A *Type II* mechanism is a surfeit of toxic substances in body fluids as a result of excess *endogenous* production or impaired degradation (or both) but not necessarily *directly* due to reduced renal excretory capacity. A *Type III* mechanism is the accumulation of toxic substances in biological fluids from *exogenous* sources by virtue of reduced renal excretory capacity often combined with continued usual dietary consumption. A *Type IV* mechanism is a deficiency or reduced activity of substances normally produced *endogenously* as a result of decreased synthesis, enhanced degradation, or biological inhibition. Combinations of more than one pathobiological process are possible. For example, urea is a putative uremic toxin that arises because of a combination of *Type I* and *Type III* processes—excessive accumulation due to impaired renal excretion and continued production due to exogenous (dietary) consumption of protein as a precursor of urea. These categories of pathobiological process are not mutually exclusive, and one may predominate over another in certain circumstances. As outlined earlier, dysbiosis of the intestinal microbiota is a very important contributor to the pathobiology of uremia, and is embraced in the Type I mechanism. PTH excess in CKD is a prime example of a Type II uremic toxicity. It is helpful to keep this classification of the processes underlying accumulation of uremic toxins in mind when approaching a patient with the uremic syndrome.

The linkage of uremic toxins to the pathobiology of uremia

In recent years a new concept has emerged that the uremic syndrome is strongly associated with a state of "chronic inflammation" and enhanced "oxidative stress" accompanying CKD that are manifested by an increase in "positive" acute-phase reactant proteins (such as C-reactive protein (CRP), Interleukin-6 (IL-6), fibrinogen, ferritin, and serum amyloid A protein) and a reduction in "negative" acute-phase reactant proteins (albumin, transferrin, and prealbumin) [1] The proposed origins of this inflammatory state include: (1) an imbalance in the body between pro- and antiinflammatory factors, (2) underlying organ-based chronic inflammation (occult infection, e.g., periodontal disease, infected vascular access, vulnerable lipid-rich atherosclerotic plaques, and localized intestinal inflammation consequent to dysbiosis, kidney inflammation associated with the underlying disease) [95], and (3) exposure to inflammatory promoters (endotoxin contaminated dialysate, bioincompatible membranes). No doubt in individual patients, multiple factors explain the presence of an inflammatory state. Certain candidate uremic toxins, such as uric acid or ADMA, may be potent promoters of inflammation. In turn, inflammation can lead to the generation of uremic toxins, such as advanced oxidation products, via the generation and inadequate scavenging of toxic oxygen radicals [1]. IS can also promote further progression of renal disease by activating harmful mediators such as Transforming growth factor beta (TGF beta) [1]. Thus the accumulation of uremic toxins may also exert a positively reenforcing action on the basic process of tissue and organ damage, in addition to contributing to the manifestations of the uremic syndrome per se [1].

The "toxicity" of ADMA has also emerged as an important element in new concepts of the pathobiology of uremia [1]. This methylated amino acid is highly protein bound, and its concentration in plasma is elevated in uremia. The elevation is predominantly caused by the inhibition of its major kidney-derived metabolizing enzyme (dimethylarginine dimethylaminohydrolase-1; DDAH-1) rather than by markedly decreased renal excretion. ADMA, along with uric acid, is a potent inhibitor of endothelial cell nitric oxide synthase (eNOS) [1]. Impaired eNOS and reduced nitric oxide production by endothelial cells may lead to vasoconstriction, elevated blood pressure, and vascular damage. Oxidative stress associated with uremia may also impair the effectiveness of DDAH-1 providing a link between endothelial cell dysfunction and inflammation in uremia [1]. DNA methylation and repair may also be adversely affected by putative uremic toxins [1]. Thus some retention uremic solutes (such as homocysteine and its metabolites) could have profound effects on gene expression and epigenetics [96].

TMAO has received substantial attention as a low-molecular-weight, polar uremic solute that promotes cardiovascular disease [97–100]. This molecule is generated from choline, betaine, and carnitine consequent to gut microbial action [101]. The blood levels are determined by diet (especially red meat) [99], the gut microbiome, drugs, and hepatic Flavin monooxygenase activity. Increased plasma levels are associated with enhanced atherogenesis and an increase in cardiovascular events. Omnivores have higher plasma levels of TMAO than vegetarians. Dietary L-carnitine (in red meat) rapidly generates γ-butyro-betaine that is then converted by microbiota to TMA and thence to TMAO [99]. Thus TMAO may be a significant uremic toxin that may be subject to manipulation by dietary interventions. Interestingly, TMAO may protect cellular proteins from the damaging effects of carbamylation from urea [100].

Thus the pathobiology biology of uremic toxicity needs to be viewed as a complex, dynamic, interacting system of effector, promoter, and inhibitory molecules occurring in a situation of reduced renal excretory capacity, impaired defensive ability, and superimposed deficiency states [3]. The cumulative adverse effects on cellular and organ system function will depend on the balance of these factors.

Clinical manifestations of uremia and the role of tropisms

The clinical manifestations of uremic toxicity are broad and diverse. As pointed out previously, every organ system in the body can be affected. Each individual uremic toxin may have its own unique profile of "tropisms," that is, each toxin may have a preferential action on only one system (monotropic) or may act on only a few systems (oligotropic). Most uremic toxins studied so far have effects on multiple systems (pleiotropic), perhaps by interference with very fundamental common pathways of cellular behavior or organelle function (nitric oxide synthesis, DNA methylation and repair, defense against oxidative stress, and mitochondrial dysfunction), such as best exemplified by PTH, uric acid, and other derivatives of purine nucleotides and ADMA. However, some toxins, such as guanidino compounds, may exhibit relative specificity for certain organ systems (hematopoiesis, neuronal function, bone metabolism, and endothelial cell integrity) [101]. Oxidized lipids, TMAO, and adipokines may have more deleterious actions on the vascular tree and insulin signaling [102,103]. Protein-bound toxins may have a predilection to produce damaging effects on the heart and cardiovascular system [104–107]. FGF-23 seems to have a major toxic effect on the myocardium [91–93], leading to left ventricular hypertrophy. Elucidation of the "tropic" behavior of individual uremic toxins is an important element in their full characterization and classification.

The effects of diet and dialysis on uremic toxins

Uremic toxins consist of a panoply of molecules, some of which are derived from dietary intake (mainly its protein constituents) and the effects of the bacterial flora (microbiome) of the gastrointestinal tract on orally ingested nutrients. Thus it is not surprising that these factors can influence the circulating levels of at least some uremic toxins. Similarly, extracorporeal/extrarenal elimination of some uremic toxins is one of the fundamental tenets of dialytic treatment of the uremic state. This section will briefly summarize current knowledge concerning the impact of these two facets of uremia and uremic toxins

Diet

Plasma concentrations of low-molecular-weight uremic solutes (such as urea and guanadino compounds) are increased in CKD, and the levels correlate with dietary protein intake and urine urea nitrogen excretion [108]. The uremic solutes (often protein bound in the circulation) that are derived from the effects of the intestinal microbiome (pCS, hippuric acid, IS, phenylacetylglutamine, and TMAO) are increased even in moderate CKD, but the intake of dietary precursors or adherence to special diets have varying effects on plasma levels of these uremic solutes [109,110]. A plant-based diet may increase the levels of these solutes and agents that influence the microbiome (probiotics, prebiotics, and synbiotics) and may decrease the levels of at least some uremic solutes, such as IS [110,111]. A low-protein diet (0.6 g/kg/d) can reduce levels of pCS and IS, possibly by influencing the gut microbiome profile [112]. Genetic modulation of gut microbiota can influence circulating uremic toxin concentrations directly [113]. This latter evidence strongly points toward the controlling effects of the gut microbiota on circulating uremic toxin levels in CKD. The characteristics of the gut microbiota are in turn influenced by the diet, especially protein and fiber [114]. Vegetarians consuming a low-protein, plant-based diet have lower production of *p*-cresol sulfate and IS compared to omnivores on a normal protein intake [115]. This has led to an increasing number of proposals for a low-protein, plant-based diet as the preferred one for patients with CKD [116,117]. However, these proposals have not yet been formally tested for efficacy in large randomized prospective clinical trials. Moreover, when careful plasma, urine, and fecal studies are performed in subjects at varying stages of CKD, the differences in plasma protein-bound uremic toxin levels cannot be explained by the generation rate by gut microbiota, suggesting that retention consequent to reduced kidney function is the main determinant of increased plasma concentrations of protein-bound uremic solutes [118]. This may not apply to all solutes and does not mean that efforts to reduce the intestinal generation of uremic toxins are without merit. As mentioned earlier, administration of alpha-keto analogs of essential amino acids along with a very low-protein diet may have salutary effects on low-molecular-weight toxin levels, but the overall value of this approach to management of the uremic syndrome needs much more investigation [119]. The excess dietary or medication intake of trace elements may have a deleterious effect on uremic manifestations. As stated earlier, aluminum is the classic example

Dialysis

No doubt exists that dialysis (hemodialysis or peritoneal dialysis) can remove low-molecular-weight, water-soluble, nonprotein-bound uremic solutes (such as urea or creatinine), and this serves as the basis of Kt/V (urea) as a standard measure of dialysis "adequacy." The situation is much less clear for protein-bound uremic solutes (reviewed in Ref. [120]). Protein-bound uremic solute levels in dialysis-treated ESRD patients are mainly related to residual renal function and are not influenced by the convective transport of dialysis [121,122]. A small short-term trial has shown only very limited impact on protein-bound uremic toxin levels when low-flux, high-flux, and postdilution hemodiafiltration are compared [123]. Techniques to enhance dialysis removal of protein-bound uremic solutes by the use of competitive inhibitors of binding are under investigation [48,124]. Reduction of uremic toxins by dialysis is important, as many of these chemicals have direct cardiovascular toxicity (such as TMAO and IS) [125]. So far, long-term outcomes on dialysis are not greatly influenced by levels of protein-bound solutes, the plasma levels of which seem to be largely governed by residual kidney function.

The use of medium cutoff dialysis membranes or hemodiafiltration improves the removal of middle molecules, such as β_2-microglobulin and free light chains, but the long-term beneficial effects of this treatment are uncertain, at best [126,127]. As stated previously, the occurrence of β_2-microglobulin amyloidosis in hemodialysis patients has been decreasing in recent decades but has not entirely disappeared [76–78].

The association of persisting volume excess (fluid overload) in kidney failure treated by dialysis with all-cause and cardiovascular mortality [128] may point to an important "uremic toxicity" effect of retained sodium and water as compared to the traditional view of "uremic toxicity" as a manifestation of retention of protein-related metabolites, exogenous or gut derived [129]. Removal of trace elements by dialysis is largely inconsequential, although iron, selenium, and zinc deficiency can occur and iron overload may develop from repeated blood transfusions or excess oral or parenteral iron. Technically, these are not uremic toxins, per se.

Summary and conclusion

An exposition of uremic toxicity requires an integrative analysis of the physicochemical properties of putative toxins (molecular size, polarity, and protein binding), an understanding of the pathobiological processes responsible for their formation and accumulation, and a mechanistic view of how they alter fundamental cellular and organ behavior. A consideration of both glomerular filtration and tubular secretion is essential for the proper understanding of levels of putative uremic toxins in the body fluids in CKD and ESRD. An explanation of how individual toxins or groups of toxins lead to clinical manifestations of uremia requires a consideration of tropism (monotropic, oligotropic, and pleiotropic toxins). This "multidimensional" integration allows for a better understanding of the complexity and the potential for mapping of the important elements of uremic toxicity. The long-term importance of a better understanding of the chemical basis of uremia is to aid the development of more effective and more rational methods of treatment, including dietary manipulation to minimize formation of toxins, ablation of organ sources of putative toxins, reduction of exogenous sources of toxic precursors, reduction in (colonic) formation, and absorption of putative toxins derived from actions of intestinal microbiota on dietary constituents (mainly proteins), enhancement of extrarenal removal of toxins (intra- or extracorporeal), supplementation for replacement of deficiencies, suppression of toxic effects at the cellular level, and replacement of renal tissue or its products. The specific roles of retained uremic toxins, derived from diet and gut metabolism, as compared to retention of sodium and water (volume overload) need to be better understood. Dietary and dialytic management of uremic toxicity is but one part of the overall picture of uremic therapeutics. Note added in Proof—Very recently, an International Consensus Conference (see Reference [130]) has revised and updated the definition and classification of uremic toxins, This timely and very comprehensive schema has been based on a "holistic" integration of the physico-chemical characteristicss and dialytic removal of the solutes retained in uremia. The focus is on linkage with clinical findings and outcomes, particularily in kidney failure treated by hemodialysis. An evidence based approach is emphasized. Recommendations for future research is also included in the presentation. This landmark conference publication is worth reading in its original form.

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CHAPTER

7

Inflammation in chronic kidney disease

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General considerations

Inflammation (Latin *inflammatio*, to set on fire) represents a complex biological response of vascular tissues to harmful stimuli. Acutely, inflammation may be considered a protective attempt by the organism to remove the injurious stimuli as well as to initiate the healing process. Whereas the acute release of proinflammatory cytokines may have beneficial effects, a chronic low-grade systemic inflammatory activity is likely to be detrimental for the organism. This is the problem faced in the uremic milieu, characterized by a state of persistent low-grade chronic inflammation, and where the persistent effect of causative stimuli leads to functional changes as well as destruction of cells and tissues.

In chronic kidney disease (CKD) and especially in end-stage kidney disease (ESKD) the systemic concentrations of both pro- and antiinflammatory cytokines are multifold higher, due to both decreased renal clearance and increased tissue production. Because of this, inflammation is a major characteristic in advanced CKD worldwide according to C-reactive protein (CRP) estimations [1–8]. Reports from the National Health and Nutrition Examination Survey III show that half of the patients with estimated glomerular filtration rates 15–60 mL/min had CRP levels >2.1 mg/L [9]. Among ESKD patients undergoing dialysis, significant geographic variation exists with Asian patients showing markedly lower inflammation compared to those from either Europe or North America (Fig. 7.1) [1–8]. Effects of chronic inflammation, via both direct and indirect mechanisms, are an important inducer of the protein-energy wasting (PEW) syndrome, cardiovascular disease (CVD), and mineral and bone disorder. The purpose of this chapter is to describe the physiopathology and implications of these complex inflammatory processes with a special focus on PEW. At the same time, we will discuss the applicability of regular CRP monitoring in the clinical setting and possible therapeutic initiatives to tackle this risk factor.

Multifactorial causes of inflammation in chronic kidney disease

There are many and varied factors, inherent or not to a reduction in kidney function, that contribute to systemic inflammation. Among these, intercurrent clinical events are likely the most important [10]. Infectious agents and microorganisms are also causative or contributory factors to the inflammatory cascade, being also associated with atherosclerosis progression [11–14]. Reductions in kidney function per se, or even small changes in residual renal function (RRF), further seem to impact on "uremic inflammation." It has, thus, been hypothesized that retention of circulating cytokines [15], advanced glycation end products (AGEs) [16], and prooxidants [17] initiate and enhance the proinflammatory milieu when kidney function declines. Additional mechanisms by which a failing kidney function may promote inflammation include volume overload, carbonyl stress [18], metabolic acidosis [19], sympathetic overactivity (and/or blunted vagal nerve activity) [20], or chronic inflammatory process associated with periodontitis [21,22].

There is also a growing body of evidence that shows alterations in the gastrointestinal tract are an important source of inflammation [23]. The intestinal microbiota is involved in the regulation of the immune system

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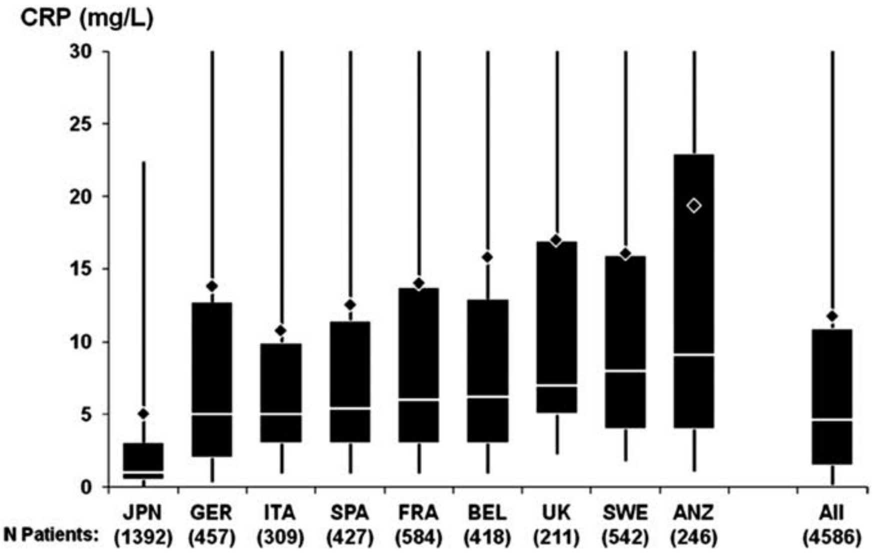

FIGURE 7.1 Distribution of CRP in different countries from the DOPPS study, restricted to patients on dialysis >90 days in facilities that routinely measure CRP ($n = 4586$). The top and bottom of the boxes indicate the 25th and 75th percentiles of the distribution. The horizontal line within the box indicates the median (50th percentile), and the diamond indicates the mean. Vertical lines extend to the 5th and 95th percentiles. *CRP*, C-reactive protein; *DOPPS*, Dialysis Outcomes and Practice Patterns Study. *Source: Reproduced with permission from Bazeley et al. Clin J Am Soc Nephrol 2011;6(10):2452–61.*

and is altered in patients with CKD and ESKD [24,25]. These alterations include a shift toward bacteria involved in the production of uremic toxins, including indole (i.e., indoxyl sulfate) and p-cresol sulfate. Furthermore, patients with CKD have reduced intestinal barrier function [26] that may increase bacterial and endotoxin translocation [27–30] and result in a strong immune response [28]. Fluid shifts and intestinal ischemia during hemodialysis (HD) may also exacerbate this translocation [31].

The HD procedure per se may further contribute to increased systemic inflammation [32] through interaction of circulating monocytes with nonbiocompatible membranes [33], blood contact with nonsterile dialysate solution [34], use of unpure dialysate [35–37], sodium tissue loading [38], the extent of convective transport, and the frequency and duration of dialysis [39,40]. However, the overall contribution of the dialysis procedure is unlikely a major instigator of inflammation because of the high prevalence of inflammation biomarkers in CKD 5 patients not yet on renal replacement therapy [41,42]. Overhydration and volume overload may, via bacterial or endotoxin translocation in patients with severe gut edema, lead to immunoactivation and increased inflammatory cytokine production [43]. Finally, strong interrelations between inflammation, RRF, and left ventricular hypertrophy have been documented in dialysis patients [4].

Obesity, a common finding in CKD patients, may also contribute to an enhanced inflammatory activity. Both truncal fat mass [44] and abdominal fat deposition [45] have been associated with increased systemic inflammation in dialysis patients. Also in nondialyzed CKD patients, longitudinal variations in abdominal fat are accompanied by parallel changes in systemic inflammation (Fig. 7.2). The reasons for this association relate to the capacity of adipocytes and fat-infiltrated macrophages to secrete adipokines, interleukin (IL)-6, or tumor necrosis factor (TNF)-α into systemic circulation [46,47]. Many adipokines exert further proinflammatory effects [48–50]; considering the dramatic effect that loss of RRF has on the clearance of adipokines, the systemic effects of adipokine imbalance in CKD patients may be even greater than in the general population. Furthermore, uremic fat may be overactivated, since proinflammatory genes have been demonstrated to be upregulated in visceral fat from CKD patients as compared to matched controls [51]. Surprisingly, a recent observational study found that the protective effect of higher BMI on mortality existed in inflamed, but not noninflamed dialysis patients [52]. As a final remark, we should emphasize that obesity, as a proinflammatory state, may also link to PEW. The concept

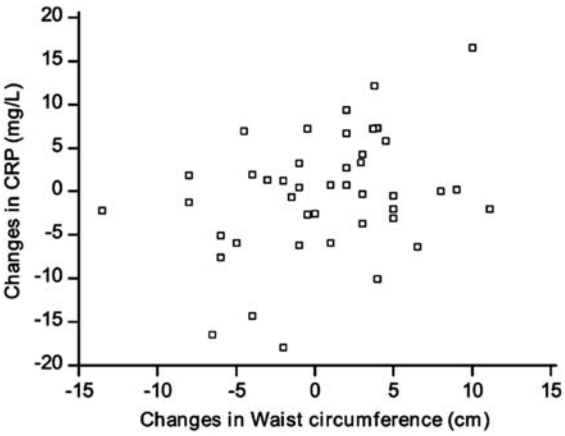

FIGURE 7.2 Direct association between 1-year variation in waist circumference and CRP levels in CKD patients stages 3–4. *CKD*, Chronic kidney disease; *CRP*, C-reactive protein. *Source: Reproduced with permission from Carvalho et al., Nephrol Dial Transplant 2012;27:1423–8.*

of obese sarcopenia demonstrated that PEW exists at any BMI categories (underweight, normal, and overweight), and that increased CRP or IL-6 levels were a feature of PEW in any given body weight [53]. This may be particularly true for abdominal obesity, which was accompanied by a higher prevalence of malnutrition and inflammation, while at the same time the patients have lower muscle mass and strength [45].

To finish, studies show that the inflamed uremic phenotype may also be the result of genetic differences, since Asian dialysis patients treated in the United States still have a markedly lower inflammation and lower adjusted relative risk of mortality than Caucasians [54]. Indeed, a substantial genetic heritability (35%–40%) has been found for CRP production [55,56], and many studies demonstrate a significant impact of genetic variations on the uremic inflammatory response [57,58]. Some paradoxical racial differences in CKD outcome may be, however, influenced by uremic inflammation: while in the general population, African-Americans experience a higher mortality rate than Caucasians, African-Americans treated with dialysis typically survive longer than Caucasians [59]. An American prospective cohort study of incident dialysis patients observed that the survival advantage among African-American dialysis patients was found to only exist in the setting of high levels of inflammation [60]. Thus racial differences in the presence and response to inflammation may underlie this long-observed survival paradox and may be worthy of further investigation. Lastly and perhaps in connection to this, shortening of telomeres (nucleoprotein complexes protecting the chromosome ends that are involved in chromosome stability and repair) has been associated with an inflamed phenotype and increased mortality in dialysis patients [61].

Inflammation as a cause of protein-energy wasting

Inflammation is an important contributory component of the complex PEW syndrome, both by direct and indirect mechanisms on muscle proteolysis, impinging upon and magnifying other causes of PEW in a vicious circle. A scheme of presentation of the mechanisms by which inflammation leads to PEW is depicted in Fig. 7.3.

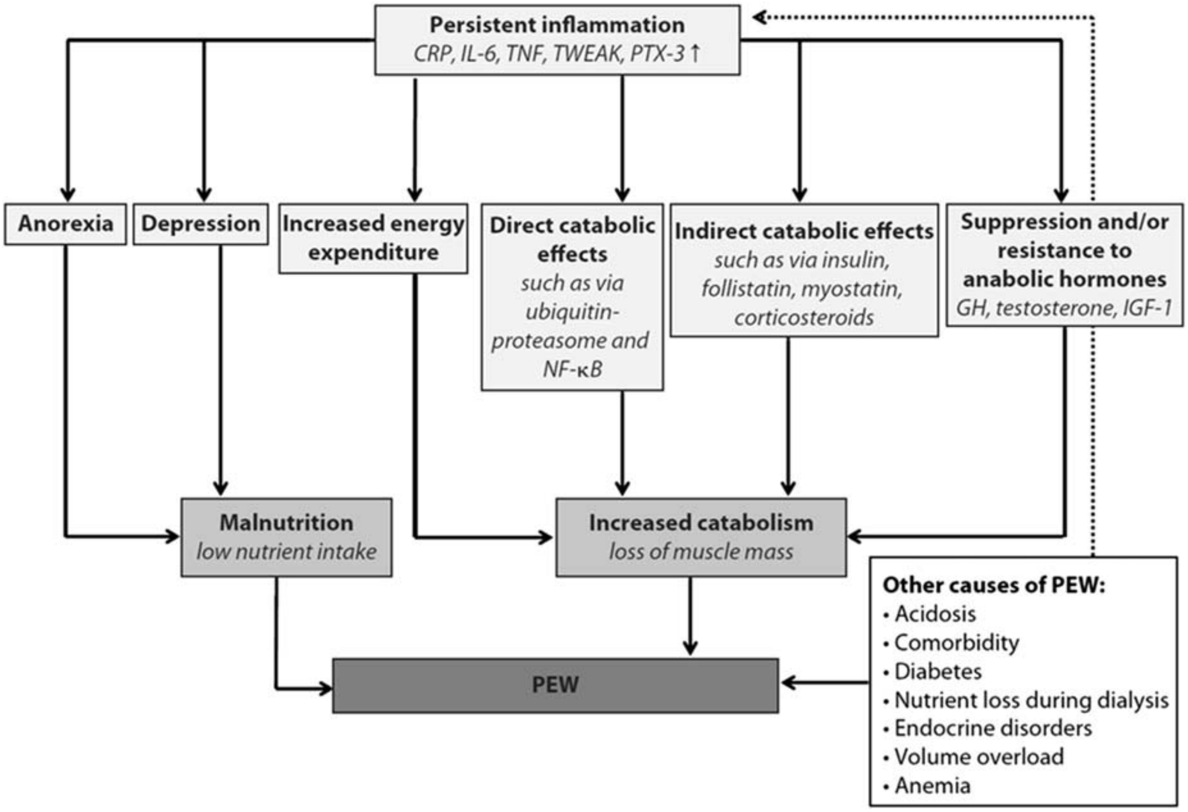
Persistent inflammation
CRP, IL-6, TNF, TWEAK, PTX-3 ↑
Anorexia
Depression
Increased energy expenditure
Direct catabolic effects such as via ubiquitin-proteasome and NF-κB
Indirect catabolic effects such as via insulin, follistatin, myostatin, corticosteroids
Suppression and/or resistance to anabolic hormones GH, testosterone, IGF-1
Malnutrition low nutrient intake
Increased catabolism loss of muscle mass
PEW
Other causes of PEW:
• Acidosis
• Comorbidity
• Diabetes
• Nutrient loss during dialysis
• Endocrine disorders
• Volume overload
• Anemia

FIGURE 7.3 Proposed mechanistic pathways by which persistent inflammation may promote protein-energy wasting via malnutrition and increased catabolism in patients with CKD. *CKD*, Chronic kidney disease. *Source: Reproduced with permission from Meuwese et al., Contrib Nephrol 2011;171:120–6.*

Inflammation leading to anorexia

Anorexia or loss of appetite is one of the initial steps leading to reduced nutrient intake in CKD, being this issue discussed in more detail in Chapter 38, Nutrition and Anemia in Chronic Kidney Disease. Cytokines and adipokines are capable of inducing anorexia by influencing meal size, meal duration, and frequency. Specific cytokines and adipokines also access the brain acting directly on hypothalamic neurons and/or generating mediators targeting both peripheral and/or brain target sites [62,63]. In fact, inflammation is a common feature accompanying the occurrence of anorexia in clinical studies of dialysis patients [64–67]. In addition, inflammation is also a feature of other pathophysiological processes related to the patient's ability and desire to eat, such as dental problems and incidence of periodontitis [21], alterations and infections in the gastrointestinal tract [68], and hypothalamic resistance to orexigenic adipokines [69]. Also olfactory function is impaired in patients undergoing HD and related with the severity of malnutrition and inflammation [70]. Because inflammation inhibits progenitor cell proliferation and olfactory regeneration [71], it can be speculated that persistent uremic inflammation may further impact the patient's desire to eat via this pathway.

Inflammation and depression

Depressive symptoms are more frequent with gradual reduction in renal function and relate to poor outcome and mortality in this and other patient groups [72–74]. Cytokines are thought to be important mediators of brain immune connection and may play an important role in the pathogenesis of depression due to their effect on neurotransmitters and neurohormones [72,75]. In patients undergoing dialysis, depressive symptoms seemed to worsen in the presence of increased IL-6 levels compared to other cytokines [76–79], and 8 weeks of fluoxetine treatment in depressed HD patients decreased serum IL-1β levels [80]. Depression may undeniably link to fatigue [81] and unwillingness to eat [82], contributing in a vicious circle to anorexia, physical inactivity [83,84], PEW, and worse outcome, all of which have also been attributed, in part, to the effects of systemic inflammation.

Inflammation and increased energy expenditure

Many of the metabolic abnormalities present during the inflammatory response, including fever, elevated oxygen consumption, enhanced lipolysis and fat utilization, increased concentration of catabolic hormones, and extensive protein catabolism, consume high quantities of energy and may account for as much as 15% of the daily energy expenditure [85]. The stimulatory effect of inflammation on energy expenditure has been suggested in various studies in nondialysis and dialysis patients, in which CRP, IL-6, and physical activity levels were important determinants of energy expenditure in these populations [4,86–88]. Because increased resting energy expenditure has been associated with high mortality rates and worse nutritional status in dialysis patients [4], the impact of increased energy expenditure on muscle mass and body fat stores needs further evaluation.

Catabolic effects of inflammation

One of the main detrimental effects of proinflammatory cytokine activation in end-stage renal disease (ESRD) patients is muscle depletion [89,90]. In animal and human studies, infusion of TNF-α, IL-1, and IL-6 leads to increased muscle protein breakdown [91–94]. Consequently, clinical studies in CKD patients have shown links between inflammatory cytokines and muscle wasting [3,15,95,96]. A main mechanism of inflammation-induced wasting is via the activation of NF-κB, ATP–ubiquitin-dependent proteolytic pathways, and caspase-3 (leading to cleavage of a characteristic 14 kDa actin fragment) that cause muscle wasting [97]. As Raj et al. [98] observed ineffective utilization of exogenous amino acids for muscle protein synthesis during HD, they hypothesized that increased skeletal muscle expression of IL-6 further augmented muscle protein catabolism in ESRD. In another study, Boivin et al. [99] reported increased caspase-3 activity (an initial step resulting in the loss of muscle protein is activated) and augmented apoptosis in uremic skeletal muscle, which may be due to increased IL-6 stimulation. TNF-α and IL-6 seem to play important roles in the processes of frailty and uremic wasting [15]; however, they may not explain the whole picture. Indeed, a recent study in HD patients showed that while semestral variation of IL-6 levels strongly predicted outcome, such IL-6 variation did not associate with body compositional changes in mixed multivariate models [100]. Other proinflammatory mediators that so far received relatively little attention in the nephrology community may concomitantly contribute: for instance, IL-15 is an immune-regulatory cytokine that exhibits proinflammatory activity by acting on a wide variety of cell types that, paradoxically, seem to have an anabolic role as the administration of IL-15 to cachectic tumor-bearing animals results in an improvement in the protein wasting process based mainly on the inhibition of protein degradation [101]. Recently, the TNF-related weak inducer of apoptosis (TWEAK) has been implicated in several biological responses, including inflammation, angiogenesis, and osteoclastogenesis. As chronic administration of TWEAK resulted in reduced skeletal muscle weight in mice with an associated increase in the activity of ubiquitin−proteasome system and NF-κB [102], upregulation of the TWEAK-Fn14 system in the context of uremia may promote PEW [103]. Finally, Zhang et al. [94] demonstrated a previously unrecognized role of serum amyloid A in acting synergistically with IL-6 to impair insulin/insulin growth factor (IGF)-1 signaling by increasing SOCS3 transcription, which results in muscle proteolysis. They proposed that angiotensin II may stimulate an interaction between the liver and the skeletal muscle because the liver becomes the major source of both IL-6 and serum amyloid A.

Inflammation and anabolic resistance

The uremic state is associated with abnormalities in the synthesis and action of many hormones, some of which may further contribute to the PEW syndrome, such as the case of erythropoietin and anemia. One of the most important procatabolic hormonal misbalances in CKD is insulin resistance, which in the general population has since long shown intimate links with systemic inflammation [104,105]. Administration of recombinant TNF to cultured cells or animals impairs insulin action, and obese mice lacking functional TNF or TNF receptors have improved insulin sensitivity compared with wild-type counterparts [106]. In accordance, chronic administration of infliximab (a chimeric of anti-TNF antibody) improves insulin resistance [107]. Although TNF increases lipolysis [108], which is highly linked to the development of insulin resistance, IL-6 inhibits insulin action both in vitro and in vivo muscle, liver, and adipocytes [109]. Overexpression of myostatin, a member of the transforming growth factor beta family of cytokines, may also inhibit insulin signaling as well as increase expression of FoxO [110,111]. Thus decreased insulin sensitivity caused by persistent inflammation can predispose to loss of muscle mass by decreasing the anabolic action of insulin on the skeletal muscle. In fact, in clinical conditions where insulin resistance develops, such as in elderly subjects and in patients with type-2 diabetes mellitus, muscle wasting is often observed. By using stable isotope tracer techniques, Pupim et al. [112] showed that HD patients with type-2 diabetes had significantly increased skeletal muscle protein breakdown as compared to nondiabetic HD patients. Also, incident dialysis patients with diabetes mellitus had significantly accelerated loss of lean body mass as compared to nondiabetics during the first year of dialysis therapy [113].

Resistance to anabolism by the growth hormone (GH)/IGF-1 axis may constitute another factor contributing to the loss of strength and muscle mass in CKD. While several clinical studies have reported that GH has a salutary effect on body composition and muscle protein synthesis in CKD patients [114], the responses to GH treatment vary considerably [115]. As inflammation inhibits GH action [116], it can be postulated that the GH response is blunted in uremia. Indeed, Garibotto et al. [117] found that although GH forearm perfusion caused a decrease in the negative potassium and protein balance of HD patients without inflammation, no such effect was seen in HD patients with inflammation. Their finding, thus, implies that a resistance to pharmacologic doses of GH is not related to uremia per se but rather to an increased inflammatory state. In addition, IL-6 administration inhibits IGF-1 secretion, further contributing to the sarcopenic process [118]. Interestingly, recombinant GH replacement therapy in CKD patients in well-designed studies has consistently been linked to improved anabolic function, stimulation of protein synthesis, decrease in urea generation, and improvement in nitrogen balance [119].

Low thyroid hormone levels in CKD patients have traditionally been interpreted either as an acute adaptation aimed at reducing energy expenditure and minimizing protein catabolism or as a chronic maladaptation participating in the wasting syndrome of prolonged critical illness [120]. Recent studies, nevertheless, associate low triiodothyronine levels in CKD stage 5 patients with systemic inflammatory markers (Fig. 7.4), endothelial dysfunction, and the prediction of all-cause and cardiovascular mortality [121−123]. Interestingly, correction of metabolic acidosis in dialysis patients is able to restore these hormonal derangements [124,125]. Several hypotheses connect the state of subclinical hypothyroidism with low-grade persistent inflammation in uremia [126]. Indeed, IL signaling downregulates the peripheral conversion of total thyroxine (T4) into triiodothyronine (T3) in both experimental [127] and clinical [128] studies. In HD patients, inflammation was accompanied by reductions in T3 levels, reverting these to normal as inflammation resolved [126]. It is, therefore, plausible that low T3 levels in ESKD represent an intermediate link between inflammation, PEW, and mortality. Indeed, a recent study showed in fact that the impact of free T3 on mortality prediction was abrogated after adjustment for CRP and albumin, taken in this study as surrogates of PEW [129].

Prolactin retention in CKD impairs the production of gonadotropic hormones. In men, this translates into a high prevalence of testosterone deficiency (male hypogonadism), with women displaying also very low

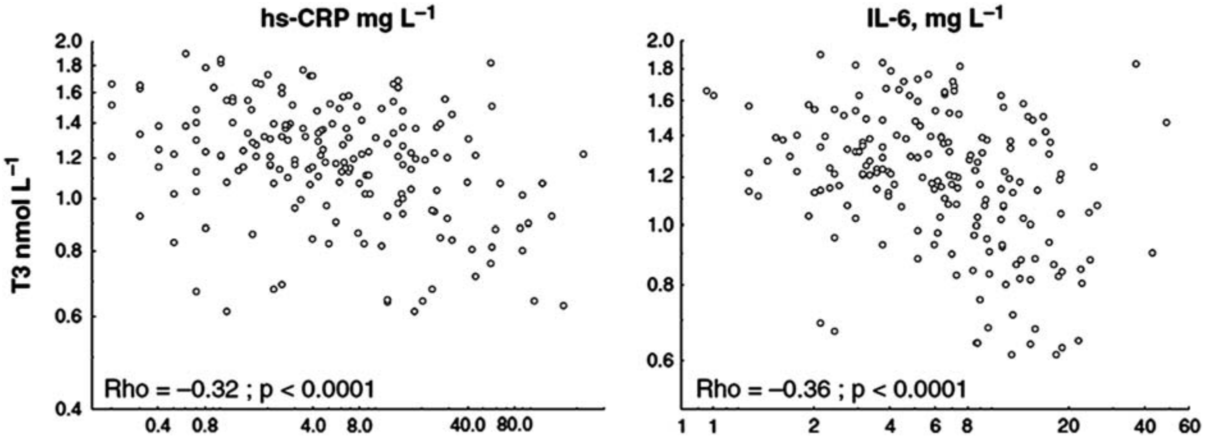

FIGURE 7.4 Strong inverse associations between total triiodothyronine (T3) levels and markers of inflammation (IL-6 and CRP) in euthyroid ESRD patients. *CRP*, C-reactive protein; *ESRD*, end-stage renal disease; *IL*, interleukin. *Source: Reproduced with permission from Carrero et al., J Intern Med 2007;262(6):690–701.*

testosterone concentrations [130–133]. Testosterone is a potent anabolic hormone that actively induces muscle protein synthesis [134]. Both muscle mass loss in wasted patients [135] and rapid weight loss during weight reduction regimens [136] have been correlated with testosterone decline. In dialysis and predialysis patients, low testosterone levels were associated with increased mortality risk [137–139], and the observation that adjustment for *S*-creatinine levels (used as a surrogate marker of muscle mass) abrogated this mortality prediction [137] may indirectly support this pathophysiological mechanism. Androgen therapy in uremic patients (alone or in combination with resistance training) has resulted in significant amelioration of both muscle mass and nutritional status [140,141].

Inflammation as a catalyst for other risk factors

Persistent low-grade inflammation in CKD may, in addition to putative direct proatherogenic and prowasting effects, serve as a catalyst and modulate the effects of other risk factors for PEW and CVD [142]. While inflammation may enhance the appearance of PEW, inflammation can also interact with malnutrition and CVD in exacerbating the mortality risk. A Dutch study demonstrated an interaction effect between these risk factors in relation to outcome [143]. The concurrent presence of inflammation, CVD, and PEW was associated with a 16 deaths/100 person-years higher mortality rate than expected from the solo effects of these features. Thus this observation translates epidemiological observations into evidence for the existence of a syndrome of PEW, inflammation, and atherosclerotic CVD [144] where the whole is more than its parts [42]. Parekh et al. [145] also reported that while sudden cardiac death was common among ESRD patients, inflammation and malnutrition significantly increased its occurrence independent of traditional cardiovascular risk factors. Specifically, across increasing CRP tertiles cross-classified with decreasing albumin tertiles, an exacerbation of the risk for sudden cardiac death was observed.

Other consequences of inflammation

There is a wealth of data linking *vascular calcification* with systemic inflammation. TNF can induce mineralization of calcifying vascular cells in vitro [146] and coculture of these cells with monocyte/macrophages can accelerate mineralization [147]. Receptor activator of NF-κB ligand (RANKL) is a membrane-bound or soluble cytokine essential for osteoclast differentiation, whereas the decoy receptor osteoprotegerin (OPG) masks RANKL activity. As both seem to influence the inflammatory component of atherosclerosis [148], it is of interest that OPG upregulates endothelial cell adhesion molecule response to TNF [149]. These findings suggest a mechanism by which OPG may stimulate inflammation in atheroma and thereby promote the progression and complications of atherosclerosis, which would agree with the observed detrimental effects on the survival of both increased inflammation and OPG levels in HD patients [150,151]. On the other hand, vascular calcification, as part of the atherosclerotic process, is due to the deposition in the arterial intima of basic calcium phosphate crystals, similar to those that mineralize bone. It was recently shown that these crystals could interact with and activate human monocyte-derived macrophages, inducing a proinflammatory state via protein kinase C and mitogen-activated protein kinase pathways [152]. This would again imply a vicious cycle of inflammation and arterial calcification that could explain the associations between inflammation and outcome in CKD. Finally, the most well-studied inhibitor of calcification is fetuin-A. In CKD, low levels of circulating fetuin-A are associated with cardiac valvular calcification, increased cardiovascular burden, and increased mortality risk [153−156]. Inflammation and PEW may be important causes of a decrease in serum fetuin-A levels in patients with CKD, as it behaves as a negative acute phase reactant [157,158].

The effects of inflammation may also be observed in the bone. Abnormal mineral metabolism may be both a cause and consequence of inflammation [159−161]. Increasing levels of dietary phosphate have been shown to increase TNF-α in a rat model of CKD [159]. Furthermore, many cytokines, including IL-6, TNF-α, and CRP, are associated with levels of fibroblast growth factor 23 [161] and IL-1 and IL-6 are associated with parathyroid hormone levels. High levels of TNF-α may stimulate RANKL and increase bone resorption through increased osteoclast activity [162] contributing to the high rates of fractures in CKD patients [163]. Finally, there is also evidence that inflammation plays a role in red blood cell formation and the development of anemia by reducing the production of erythropoietin [164], contributing to erythropoietin resistance [165], and reducing iron availability through the increased production of hepcidin [166].

Monitoring inflammation

CRP has in the clinical setting aroused as the prototypic marker of inflammation due to its reliability, low cost, and wide availability. The key points to consider when monitoring inflammation in the clinical setting are, however, the reasons why CRP needs to be measured and the likelihood that diagnostic and therapeutic strategies might change on the basis of these test results. Despite a decade of extensive research on the causes and effects of uremic inflammation, no randomized trials with testing of inflammatory markers as the primary intervention have been performed, nor have cost-effectiveness analyses been completed to assess additional costs or cost savings through the use of such tests. Consequently, the following suggestions about the routine monitoring of inflammatory markers are not evidence-based.

Monitoring inflammation for prognostic purposes

Prospective epidemiological studies in CKD, dialysis, or kidney transplant patients [42,167−175] have all consistently shown that a single measurement of inflammatory biomarkers are independent predictors of poor outcomes. There is nevertheless an elevated biological intra- and interindividual variability for inflammatory mediators in the setting of CKD, even more for the unspecific CRP responses. While a decreased renal function, an increased number of comorbidities, PEW, and the uremic environment (oxidative stress, accumulation of AGEs, etc.) affect interindividual inflammatory variability [176], intraindividual variation may be further exacerbated by intercurrent clinical events, type of vascular access, membrane bioincompatibility, dialysate backflow, endotoxemia, and the intermittent presence of dialysis [40,68,177,178]. Volume status, fluid intake, and RRF are also associated with this phenomenon [179]. Although it appears essential to understand and evaluate inflammation in the context of its variability as disease evolves, few studies address the consequences of regular monitoring of inflammatory markers on outcome. Of those, it seems apparent that the average of serial measurements of CRP or IL-6 provides a better survival prediction than single measurements [68,180]. Patients with a persistent CRP or IL-6 elevation during a specific time period exhibit worse outcome than those with persistent low levels or those increasing their CRP value [1,181] (Fig. 7.5).

At present, there is insufficient evidence to support the regular monitoring of inflammation in the clinic with regards to mortality prediction. The recent study from Bazeley et al. [7] demonstrated, however, that CRP may have prognostic value beyond that provided by traditional risk factor algorithms (Framingham). The inclusion of CRP in such 1-year mortality prediction model contributed to correctly reclassify 13% of the patients with regards to their risk. Thus these results can make it possible to create specific algorithms for short-term mortality prediction in CKD patients. Whether this may have prognostic applicability is not yet evident, but such algorithm could represent a decision tool toward the implementation of more aggressive therapeutic approaches in dialysis patients at risk.

Monitoring inflammation for diagnostic purposes

Probably the most useful indication of CRP monitoring is the screening and detection of underlying inflammatory processes and the assignment of appropriate treatment [182]. Possible underlying inflammatory processes include graft- or catheter-related infections, peripheral arterial disease, silent coronary ischemia, ulcers, inflammatory bowel disease, malignancies, periodontitis, or hepatitis. According to

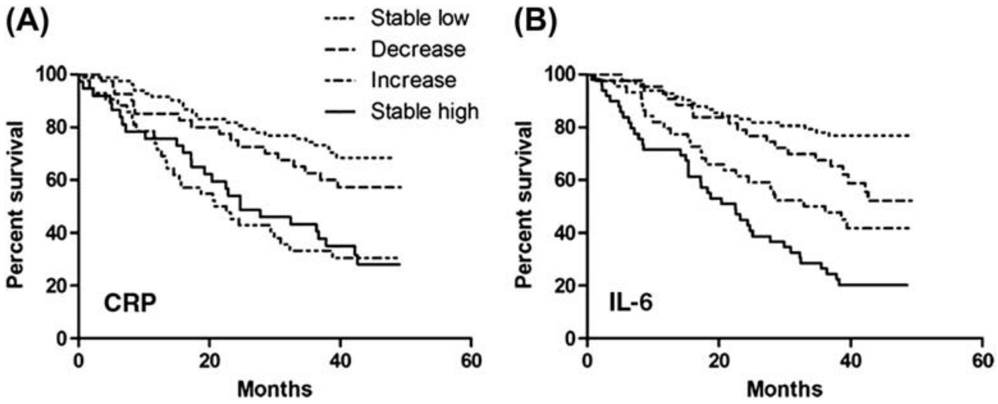

FIGURE 7.5 Persistent elevation of (A) CRP and (B) IL-6 in hemodialysis patients during a 3-month monitoring was associated with increased risk of mortality. *CRP*, C-reactive protein; *IL*, interleukin. *Source: Reproduced with permission from Meuwese et al., Nephrol Dial Transplant 2011;26(4):1313–8.*

AHA/CDC recommendations, a second CRP measurement taken 2 weeks after the first might be useful in identifying transient processes while reducing biological variation in usual clinical practice. A careful patient monitoring is warranted as well after these processes are resolved, as it has been reported that during the 30 days following an infection-related hospitalization in dialysis patients, the risk of cardiovascular events increases by 25% [183]. Patients showing CRP elevations over short periods of time should undergo an extensive clinical workup, whether they exert clinical symptoms or not. Other seemingly valid reasons for performing serial CRP measurements could be to motivate individuals at risk of inflammation to improve their lifestyles (such as smoking cessation, dental care, dietary modification, exercise, and weight loss) or to comply with drug therapies. Clearly, persistent CRP elevations or increases in inflammatory biomarkers indicate patients at high risk of dying, and major efforts should be made to address the causes of such elevations.

Treatment of inflammation in chronic kidney disease

Few randomized controlled trials have been successful in managing inflammation in patients with CKD and no sufficiently powered randomized controlled trials targeting uremic inflammation as a means of improving morbidity and mortality in CKD patients have yet been performed. Nor is there evidence that by improving systemic inflammation, nutritional status is restored. Therefore the following recommendations for treating inflammation in patients with CKD reflect the authors' opinion. Based on the concept that inflammation plays a pivotal role in the development of the uremic phenotype, circulating inflammatory markers have the potential to be primary targets for novel treatments, including not only specific antiinflammatory therapies but also various antioxidative and antiwasting approaches.

When preexisting complications (including dialysis-related causes and smoking) have been excluded as a cause of persistent inflammation, some interventional approaches could be cautiously considered, including strategies to modify physical activity [184,185], cognitive behavior [186], and modifying the diet [187,188], including the use of bioactive nutrients with immune properties [189–194].

Certain medications have nonspecific immunomodulatory effects on CKD. For instance, in inflamed patients with moderate CKD, rosuvastatin treatment reduced CRP levels and improved both cardiovascular events and all-cause mortality [195]. In contrast, data on the effects of statins on inflammatory biomarkers in ESKD are not that consistent [196,197]. Cholecalciferol supplementation may also have antiinflammatory properties in CKD patients [198,199]. Sevelamer, which possesses AGE- and lipopolysaccharide-binding properties, is associated with a reduction in circulating CRP and endotoxin levels as well as amelioration of endothelial dysfunction [200–202]. Angiotensin converting enzime inhibitors/angiotensin receptor blocker [203–205], aliskiren (a direct renin inhibitor) [206], or allopurinol [207] have also shown suppressive effects on inflammatory markers. Among the currently available anticytokine therapies, etanercept, a TNF-receptor antagonist, was tested targeting uremic persistent inflammation in a small number of patients on HD, primarily aiming at an improvement in nutritional profiles [208]. Forty-four weeks of treatment with etanercept showed positive effects on albumin and prealbumin levels compared to the placebo group with no occurrence of adverse events, while the treatment resulted in a nonsignificant change in CRP and IL-6 [208]. Anakinra, a recombinant human IL-1-receptor antagonist, lowered plasma CRP and IL-6 levels in patients with type-2 diabetes [209]. In a recent small prospective controlled trial [210], 22 patients with markers of inflammation on HD were randomized to anakinra or placebo over 4 weeks. As those who received treatment showed a 53% reduction in CRP, 40% reduction in IL-6 levels, and 23% increase in mean prealbumin, further studies are needed to evaluate the impact of such therapy on outcome in this patient group. Finally, it should be recognized that persistent inflammation might impact on drug metabolism as inflammation is able to downregulate multiple P450 enzymes [211]. Indeed, a study showed a strong correlation between CRP levels and CYP3A4 activity (assessed by alprazolam 4-hydroxylation) in a small group of HD patients [212]. How this may affect the metabolism of commonly used drugs in CKD deserves further study.

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CHAPTER

8

Catalytic (labile) iron in kidney disease

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Introduction

Despite advances in understanding the pathophysiology of acute kidney injury (AKI) and chronic kidney disease (CKD), treatment for kidney disease remains unsatisfactory. In this chapter, we briefly recount the importance of AKI and CKD, then provide a brief description of labile iron, and, finally, summarize the role of labile iron in acute and CKD. This focus on iron is particularly relevant because of the availability of iron chelators to potentially provide new therapeutic tools to prevent and/or treat kidney disease.

Several recent studies highlight the clinical relevance of AKI. AKI has been shown to be an independent risk factor for morbidity and mortality, and even a modest increase in serum creatinine (0.3 mg/dL) is associated with high in-hospital mortality [1]. Recent studies indicate that AKI is an important determinant of posthospital discharge mortality [2,3] as well as end-stage kidney disease (ESKD) [4,5]. The suggested new definition of AKI and the rationale behind it is detailed in the publication [6] resulting from a consensus conference under the auspices of the Acute Kidney Injury Network, in which over 20 global societies representing both nephrologists and intensive care physicians participated.

CKD is a global public health problem that affects approximately 10%–15% of the adult population [7,8] and is associated with a high prevalence of cardiovascular disease [9] and high economic cost [10]. The expected marked increase in diabetes, the most common cause of CKD; increasing incidence of ESKD despite the use of angiotensin receptor blockers (ARBs); and the multiplier effect of CKD on cardiovascular disease, all point to a major challenge facing health-care systems worldwide. Despite promising results [11], a phase 3 trial for a novel treatment for diabetic nephropathy was unsuccessful [12]. While there are promising new therapeutic approaches, such as sodium–glucose-*co*-transporter-2 inhibitors to retard progression of diabetic CKD and reduce cardiovascular mortality [13], there is continued urgent need for new therapeutic modalities for halting progression of kidney disease.

Definition of catalytic (labile) iron and its importance in tissue injury

Iron is the most abundant transitional metal in the body (Table 8.1). The term "labile iron pool" was proposed in 1946 by Greenberg and Wintrobe [14] and reintroduced by Jacobs in 1977 as a "transient iron pool" to denote a low-molecular-weight pool of weakly chelated iron that passes through the cell. The term "chelatable iron" is also used, as most methodological approaches for detection of this pool of iron ions are based on the use of metal chelators [15]. Critical to iron's importance in biological processes is its ability to cycle reversibly between its ferrous and ferric oxidation states. This precise property, which is essential for its functions, also makes it very dangerous, because free iron can catalyze the formation of free radicals that can damage the cell through lipid peroxidation. *Thus from a pathophysiological standpoint, the broadest definition of a labile iron pool is that it consists of chemical forms that can participate in redox cycling and is therefore often referred to as catalytic iron* [16].

Our bodies contain as much as 3–5 g of total iron, but the pool of labile iron that can be measured [16,17] is estimated to be less than 70–90 mg. Although the existence of a cellular pool of metabolically labile iron proved controversial, the development of iron-sensitive fluorescent probes has provided much evidence in favor

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TABLE 8.1 Catalytic (labile) iron.

What is catalytic iron?
• A transient iron pool of low-molecular-weight, weakly chelated iron that passes through the cell • The broadest definition of LIP is that it consists of chemical forms that can participate in redox cycling (catalytic iron) • LIP is less than 3% (70–90 mg) of total cellular iron (3–5 g)
Evidence for its participation in disease states:
• LIP (catalytic iron) is increased in disease states • Iron chelators have a protective effect, establishing a cause–effect relationship
Catalytic iron is a common theme of cellular injury in disease states of:
• Acute and chronic kidney disease • Acute myocardial infarction • Neurodegenerative disorders

LIP, Labile iron pool.

of intracellular labile pools [18]. In most cells iron homeostasis consists of iron uptake, utilization, and storage. The process of iron uptake is carried out by a transferrin receptor and the divalent metal transporter 1 (also called DCT1; NRAMP2), whereas ferritin is an intracellular iron-sequestering protein. Recent studies are beginning to yield information on the pathways of iron transport, its export from the cell via the divalent iron ion exporter ferroportin 1 [19] and its regulatory mechanisms by hepcidin, the master regulator of iron homeostasis [20]. Since uptake and storage of iron is carried out by different proteins, the pool of accessible iron ions constitutes a crossroad of metabolic pathways of iron-containing compounds.

Probes for labile iron are comprised of a fluorescent reporter group coupled to a high-affinity iron (II or III) chelator. The fluorophore responds to metal binding by undergoing a change in fluorescence. The most commonly used fluorophores include fluorescein and rhodamine derivatives attached to a chelator (reviewed in Ref. [21]). A complementary approach for estimating cellular labile iron is based on metal-driven catalysis of oxidant formation [22]. The advantages of this method are high sensitivity and selectivity for redox-active labile iron. Studies using a variety of methods have begun to define intracellular distribution of labile iron (for reviews see Kruszewski [15] and Esposito [21]).

In vivo, most of the iron is bound to heme or nonheme protein and does not directly catalyze the generation of hydroxyl radicals or a similar oxidant [15]. Catalytic iron can be measured by various assays, including the bleomycin-detectable iron assay, which is based on the observation that the antitumor antibiotic bleomycin, in the presence of iron salt and a suitable reducing agent, binds to and degrades DNA with the formation of a product that reacts with thiobarbituric acid to form a chromogen. Thus the assay detects iron complexes capable of catalyzing free-radical reactions in biological samples [23,24]. The binding of the bleomycin–iron complex to DNA makes the reaction site-specific and antioxidants rarely interfere. The bleomycin assay detects only "free" iron and not iron bound to specific transport proteins or enzymes. The ability of iron to participate in redox cycling makes it potentially hazardous by enabling it to participate in the generation of powerful oxidant species such as hydroxyl radical (metal-catalyzed Haber–Weiss reaction, next) and/or reactive iron–oxygen complexes such as ferryl or perferryl ion [16]. In several systems the amount of free-radical generation is related to the amount of labile iron present [17].

$$
\begin{array}{lcl}
Fe^{3+} + O_2^{\bullet} & \longrightarrow & Fe^{2+} + O_2 \\
Fe^{2+} + H_2O_2 & \longrightarrow & Fe^{3+} + OH^- + OH^{\bullet} \\
\hline
O_2 + H_2O_2 & & O_2 + OH^- + OH^{\bullet}
\end{array}
$$

Iron also has a major role in the initiation and propagation of lipid peroxidation, either by catalyzing the conversion of primary oxygen radicals to hydroxyl radicals or forming a perferryl ion. In addition, iron can directly catalyze lipid peroxidation, the oxidative reaction of polyunsaturated lipids, by removing hydrogen atoms from polyunsaturated fatty acids in the lipid bilayers of organelle membranes [16]. Lipid peroxidation products, such as doubly or triply oxidized phosphatidylethanolamine (PE), have been identified to be the key executors of iron-induced cell death, also called ferroptosis. Generic or pharmacological suppression of acyls-arachidonoyl and adrenoyl esterification into PE through inhibition of acyl-CoA synthase 4 acts as a specific ferroptosis rescue pathway. Lipoxygenase (LOX-5 and LOX-15) generates doubly and triply oxygenated (15-hydroperoxy)-diacylated PE species, which also act as ferroptotic death signals; tocopherols and tocotrienols (vitamin E) that suppress LOX protect against ferroptosis, suggesting a homeostatic antiferroptosis role for vitamin E [25].

The pathological effects of iron accumulation in tissue in iron-overload states, such as are described in thalassemia patients, are well known. What is new in the field is the recognition that iron plays an important role in the pathophysiology of tissue injury in the absence of systemic iron overload. There appear at least two distinct pathophysiological mechanisms for the accumulation of labile or catalytic iron that participate in tissue injury. It is now known that specific defects in cellular iron metabolism and/or an increase in labile iron may be important in several disease processes not associated with iron overload [18,26]. For example, in Friedreich's ataxia, a neuromuscular disorder, the deficiency of the iron-chaperone protein frataxin results in improper processing of iron for heme and iron–sulfur cluster formation, leading to accumulation of iron in the mitochondria [27]. In some other neuromuscular disorders, deficiencies in pantothenate kinase, a key enzyme in coenzyme A synthesis, lead to iron depositions and brain damage [26]. In addition to these specific defects in cellular iron, there is compelling evidence that increased labile iron from several subcellular sources participates in tissue injury in a variety of disease states.

There are two broad lines of evidence for the role of labile iron in disease states: that it is increased in disease states and that iron chelators provide a protective effect, thus establishing a cause–effect relationship (Table 8.1). This has been demonstrated in many disease states, including acute and CKD, acute myocardial infarction, and neurodegenerative disorders [27]. Thus its role in disease processes appears to be a common theme of cellular injury.

Role of catalytic iron in acute kidney injury

Catalytic iron in myoglobinuric acute kidney injury

During the Battle of Britain, Bywaters and Beall described the first causative association of AKI with skeletal muscle injury with release of muscle cell contents, including myoglobin, into plasma (rhabdomyolysis) [28]. Since then, the spectrum of etiologies for rhabdomyolysis, myoglobinuria, and renal failure has been expanded with the recognition of both traumatic and nontraumatic causes [29]. The most widely used model of myoglobinuric AKI is produced by subcutaneous or intramuscular injection of hypertonic glycerol [30].

There is a marked and specific increase in catalytic iron content in myoglobinuric AKI [31]. An iron chelator provides a protective effect on renal function and is associated with a significant reduction in histological evidence of renal damage [32]. Paller also demonstrated that deferoxamine treatment is protective in three models of myoglobinuric renal injury, hemoglobin-induced nephrotoxicity, glycerol-induced AKI, and a combined renal ischemia/hemoglobin insult [33]. Similarly, Zager in his studies demonstrated the protective effect of an iron chelator in myohemoglobinuric injury [34]. Taken together, the increase in catalytic iron as well as the histological and functional protective effect of an iron chelator implicates a role for labile iron in glycerol-induced AKI.

The prevailing dogma is that myoglobin from the muscle serves as an important source of iron in glycerol-induced AKI. This is not surprising because myoglobin released from injured muscles is rich in heme iron. An alternative or additional potentially rich source of iron is cytochrome P450 (CYP), first described to play a role in reperfusion injury of the lung and kidney [35]. Cytochrome P450 is a heme-containing enzyme that can generate reactive oxygen metabolites during the oxidative metabolism of exogenous and endogenous compounds. Baliga et al. have shown that cytochrome P450 may be a significant source of iron in this model of AKI [31]. H-ferritin is a critical molecule that sequesters intracellular iron. In a recent study, deletion of H-ferritin in renal proximal tubule resulted in worse rhabdomyolysis-associated kidney injury, further suggesting an important role iron in AKI [36].

Catalytic iron in cisplatin-induced nephrotoxicity

Cisplatin is a widely used antineoplastic agent with nephrotoxicity as a major side effect. The underlying mechanism of this nephrotoxicity is still not well known. Baliga et al. have examined the catalytic iron content and the effect of iron chelators in an in vitro model of cisplatin-induced cytotoxicity in LLC-PK$_1$ (renal tubular epithelial) cells and in an in vivo model of cisplatin-induced AKI in rats [37]. The exposure of LLC-PK$_1$ cells to cisplatin results in a significant increase in catalytic iron released into the medium. Concurrent incubation of LLC-PK$_1$ cells with iron chelators, including deferoxamine and 1,10-phenanthroline, significantly attenuates cisplatin-induced cytotoxicity as measured by lactate dehydrogenase release. Bleomycin-detectable iron content is also markedly increased in the kidney of rats treated with cisplatin. Similarly, administration of deferoxamine in rats provides marked functional (as measured by blood urea nitrogen and creatinine) and histological protection against cisplatin-induced AKI [37]. Further support comes from the observation that deletion of H-ferritin in renal proximal tubule resulted in worse cisplatin-induced kidney injury [36].

Baliga et al. also have shown that cytochrome P450 may serve as a significant source of catalytic iron in cisplatin-induced nephrotoxicity [38]. Utilizing CYP2E1null (CYP2E1−/−) mice, Liu and Baliga have demonstrated a pivotal role of CYP2E1 in cisplatin-induced nephrotoxicity [39]. Incubation of CYP2E1−/− kidney slices with cisplatin results in a significant decrease in the generation of reactive oxygen metabolites and attenuation of cytotoxicity as compared to that of wild-type mice (CYP2E1+/+). CYP2E1null mice had marked functional and histological protection against cisplatin-induced renal injury, thus demonstrating the importance of cytochrome P450 2E1 in cisplatin nephrotoxicity. More recently, studies have confirmed the ability of cisplatin to induce ferroptosis [40]. Taken together, these data support a critical role for iron in mediating tissue injury via hydroxyl radical (or a similar oxidant) in this model of nephrotoxicity.

Catalytic iron in gentamicin nephrotoxicity

Nephrotoxicity is a major complication of the use of aminoglycoside antibiotics (including gentamicin), which are widely used in the treatment of Gram-negative infections. The precise mechanism(s) of gentamicin nephrotoxicity remains unknown.

Gentamicin-induced mobilization of iron from renal cortical mitochondria

In vivo, most of the iron is bound to heme and nonheme proteins and does not directly catalyze the generation of the hydroxyl radical; the source of iron available to participate in this process is uncertain. Based on the ability of superoxide to release iron from the iron-storage protein ferritin (which normally provides a secure means of storing iron in an inert form), ferritin has been suggested as a possible source of iron for the generation of powerful oxidant species. A source of iron not previously considered is iron-rich mitochondria, which contain heme as well as nonheme iron.

Ueda et al. examined whether gentamicin enhances the release of iron from renal cortical mitochondria and, if so, whether gentamicin induces iron mobilization from mitochondria directly or through the generation of hydrogen peroxide [41]. Rat renal mitochondria incubated with gentamicin results in a time- and dose-dependent iron release as measured by the formation of the iron−bathophenanthroline complex FeII(BPS)3. Based on a previous study that gentamicin enhances the generation of hydrogen peroxide by renal cortical mitochondria, Ueda et al. examined whether the effect of gentamicin on iron release is mediated by hydrogen peroxide. Catalase (which decomposes hydrogen peroxide), as well as pyruvate, a potent scavenger of hydrogen peroxide, prevents gentamicin-induced iron mobilization, indicating that gentamicin-induced iron mobilization from mitochondria is mediated by hydrogen peroxide. Direct addition of hydrogen peroxide to mitochondria results in release of iron. These results demonstrate that gentamicin induces the release of iron from mitochondria and that this is mediated through the generation of hydrogen peroxide. In recent studies, aminoglycoside-induced bacterial cell death was shown to depend on destabilization of mitochondrial iron−sulfur (Fe−S) clusters generating Fenton chemistry [42,43]. A similar oxidative mechanism might operate in aminoglycoside-induced renal- and ototoxicity. These results indicate that mitochondria should be considered a potential source of iron for the generation of other oxidant species or initiation of lipid peroxidation in other models of tissue injury.

Evidence suggesting a role for iron in gentamicin-induced acute renal failure in rats

In vitro and in vivo studies indicate enhanced the generation of hydrogen peroxide and release of iron in response to gentamicin. Most, if not all, of the hydrogen peroxide generated by mitochondria is derived from the dismutation of superoxide. Thus the enhanced the generation of hydrogen peroxide by gentamicin suggests that superoxide anion production is also increased. Superoxide and hydrogen peroxide may interact (with trace metals such as iron as the redox agent) to generate highly reactive and unstable oxidizing species, including the hydroxyl radical. Several studies have in fact shown that agents that enhance the generation of hydrogen peroxide and superoxide anion by mitochondria also enhance the generation of the hydroxyl radical. Walker and Shah demonstrated that hydroxyl radical scavengers and iron chelators provide a marked protective effect on renal function in gentamicin-induced acute renal failure in rats [44]. In addition, histological evidence of damage is markedly reduced by the interventional agents. Studies from other laboratories have provided support for these observations. Administration of superoxide dismutase or the oxidant scavenger dimethylthiourea provided a marked protection against gentamicin-induced impairment of renal function and lipid peroxidation, and dimethylthiourea attenuated tubular damage [45]. In contrast, it has been reported that, despite amelioration of gentamicin-induced lipid peroxidation by treatment of the antioxidant diphenylphenylenediamine, it failed to prevent nephrotoxicity [46]. However, it was also demonstrated that coadministration of antioxidants vitamin E and selenium is protective against gentamicin-induced nephrotoxicity [47]. It is not clear why the contradictory results are obtained; however, one explanation is that it may be due to the difference in the mechanisms for protective effect of antioxidants. Additional support for a role of iron-catalyzed free-radical generation has been provided by demonstrating that gentamicin-induced the generation of hydroxyl radicals is reduced by iron chelators in vitro [48] and iron supplementation enhances gentamicin nephrotoxicity in vivo [49,50]. Iron depletion might mediate protection through its ability to reduce the activity of the iron–sulfur cluster containing complexes [51] and thereby Fenton chemistry. Taken together, it appears that reactive oxygen metabolites and catalytic iron play an important role in gentamicin nephrotoxicity.

Catalytic iron in contrast media–associated nephrotoxicity

Rajapurkar et al. in a preliminary study have reported that kidney donors undergoing either an intravenous pyelogram or a renal arteriogram have a marked increase in urinary catalytic iron accompanied by evidence of tubular injury as reflected by an increase in urinary alkaline phosphatase and *N*-acetyl-β-glucosaminidase [52]. Since the effect of labile iron is to increase oxidative stress, it is of interest that there is good experimental evidence for the role of oxidants in contrast-induced AKI [53–55]. More importantly, in human studies, Efrati et al. reported a mean increase of 28% in urinary F2-isoprostane levels after coronary angiography [56]. Drager et al. collected urine samples for urinary F2-isoprostane (a marker of oxidative stress) immediately before and after cardiac catheterization and reported a several-fold increase in urinary F2-isoprostane in the control group after contrast exposure [57].

While these human studies indicate an association between catalytic iron and oxidative stress with contrast-induced nephropathy, they do not establish a cause–effect relationship. There is paucity of animal models of contrast-induced AKI [58]. Vari et al., utilizing a model in rabbits that they have developed [59], examined the effect of an iron chelator on renal function. An infusion of contrast media was associated with a significant decrease in creatinine clearance, which was prevented in rabbits pretreated with an iron chelator, suggesting an important role of catalytic iron in this model (Table 8.2) [60]. In a recently established murine model, volume depletion alone resulted in a rise in the serum creatinine level, in wild-type mice; iodinated contrast (Ioversol)–induced further worsening of AKI with a greater increase in serum creatinine at 72 hours. In this study, renal infiltration of macrophages, activation of inflammasomes, and interleukin-1 were shown to be critical for contrast-induced AKI [61]. Iron chelation with deferiprone has been shown to target macrophage metabolism to reduce inflammatory responses, including interleukin-1 release [62]. Collectively, these studies indicate a macrophage-dependent antiinflammatory mechanism for the protective effect of iron chelation in contrast-induced AKI.

TABLE 8.2 Animal model of contrast-induced nephropathy.

	Group 1 saline only		Group 2 DFO	
	Pre	**Post**	**Pre**	**Post**
CCR (mL/min)	8.64 ± 1	4.96 ± 1.5*	11.6 ± 1.5	10.2 ± 1.6

*$P \leq 1$; pre- versus postcontrast infusion.

Catalytic iron in ischemia–reperfusion injury

Ischemia–reperfusion is an important cause of AKI. In this section, evidence for the role of labile iron in this injury is reviewed. In addition, we briefly describe the role of labile iron in cardiac ischemia–reperfusion injury to provide supportive evidence for these mechanisms in cellular injury.

Iron has been demonstrated to accumulate in renal proximal tubules following experimental ischemia–reperfusion injury [63]. More importantly, Baliga et al. have shown a marked increase in labile iron after ischemia–reperfusion injury [64], and an iron chelator has been shown to be protective [65,66]. Additional evidence for the role of iron in ischemia–reperfusion injury comes from reports that other types of iron-binding and/or iron-translocating compounds also provide protection against ischemia. The amount of circulating redox-active iron has been shown to increase significantly in an experimental model of ischemia–reperfusion injury, and an infusion of apotransferrin (but not iron-saturated apotransferrin) results in a dose-dependent improvement in renal function following reperfusion [67]. In addition, the recent discovery of neutrophil gelatinase–associated lipocalin (NGAL), which is an important iron-transporting and iron-translocating compound, provides additional evidence for the importance of iron in AKI [68]. The biology of NGAL is complex and incompletely defined, but it is important in renal development in that it stimulates the epithelial cell phenotype, is proapoptotic, and is an iron-binding and iron-transporting protein [69]. Furthermore, NGAL is one of the most upregulated genes and proteins in the kidney following ischemic insult [68], and infusion of NGAL protein has been demonstrated to be protective of renal ischemia–reperfusion injury [69].

During experimental cardiac ischemic injury, there is a 30-fold increase in labile iron [70]. This increase in the cellular labile iron pool is mediated primarily by

TABLE 8.3 Catalytic iron in kidney disease.

Catalytic iron and oxidants in models of acute kidney injury	
Model	**References**
Rhabdomyolysis	[31–34]
Cisplatin	[36–40]
Gentamicin	[41–51]
Contrast	[52–58,60–62]
Ischemia/reperfusion	[35,63–69,76,77]

the release of iron from ferritin and is associated with severe oxidative stress, which in turn further increases levels of cellular labile iron [70–72]. Therapeutically, both deferiprone and deferoxamine have been demonstrated to protect against experimental cardiac ischemia–reperfusion injury [73–75]. Iron loading has been demonstrated to further increase cardiac ischemia–reperfusion injury and again deferoxamine is protective, even in the iron-overloaded state [73]. Hepcidin is a master regulator of iron homeostasis through its ability to downregulate ferroportin and thereby induce H-ferritin-dependent intracellular iron sequestration. Scindia et al. demonstrated that preadministration of hepcidin induced hepatosplenic iron sequestration, increased splenic and renal H-ferritin expression, and prevented renal ischemia–reperfusion injury in mice [76]. In a recent study, Leaf et al. demonstrated that plasma catalytic iron levels predict the risk of AKI and mortality after cardiac surgery [77]. Further, deferoxamine has also been shown to improve outcomes in man following coronary artery bypass graft surgery [78]. Taken together, the body of scientific and clinical data supporting the importance of the role of iron in the pathogenesis of ischemic injury is compelling. The role of catalytic iron and oxidants in AKI is summarized in Table 8.3.

Catalytic iron in chronic kidney disease

Catalytic iron in experimental glomerular disease

The role of iron has been examined in several models of leukocyte-dependent and -independent models of glomerular disease [79] (Table 8.3). The antiglomerular basement membrane antibody is a well-characterized model of complement- and neutrophil-dependent glomerular injury. In this model in rabbits, Boyce et al. reported that an iron chelator significantly attenuates proteinuria [80]. In addition to proliferative glomerulonephritis, the ability of glomerular cells to generate oxidants suggests that they may act as important mediators of injury in glomerular diseases that lack infiltrating leukocytes. An animal model of minimal change disease is induced by a single intravenous injection of puromycin amino nucleoside. Catalytic iron (measured as bleomycin-detectable iron) is markedly increased in glomeruli from nephrotic rats, and an iron chelator prevents an increase in catalytic iron in the glomeruli and provides complete protection against proteinuria, suggesting an important pathogenic role for catalytic iron in this model [81,82].

Baliga et al. have demonstrated that cytochrome treatment of PAN resulted in a marked increase in catalytic iron associated with significant loss of glomerular cytochrome P450 content. Administration of CYP inhibitors significantly prevented injury-induced loss of CYP content and increase in catalytic iron in the glomeruli accompanied by a marked decrease in proteinuria [83]. In an in vitro study using glomerular epithelial cells, CYP inhibitors also markedly prevented a PAN-induced increase in catalytic iron and hydroxyl radical formation accompanied by significant protection against PAN-induced cytotoxicity. Taken together, these data indicate that CYP, a group of heme protein, may serve as a significant source of this catalytic iron. In addition, they have shown with in vivo and in vitro studies that cytochrome P450 2B1, an isozyme present in the glomerulus, is a source of catalytic iron that participates in glomerular injury in this model [84,85].

Passive Heymann nephritis, induced by a single intravenous injection of anti-Fx1A, is a complement-dependent model of glomerular disease that resembles membranous nephropathy in humans. The administration of an iron chelator markedly reduces proteinuria, suggesting the role of labile iron in passive Heymann nephritis [86]. Baliga et al. have shown that feeding an iron-deficient diet provides the protection in this model [87].

Role of iron in experimental progressive kidney disease

The severity of tubulointerstitial injury is a major determinant of the degree and rate of progression of renal failure. The data supporting the role of iron in models of progressive renal disease consist of demonstration of increased iron in the kidney; enhanced oxidant generation, which provides a mechanism by which iron can be mobilized; and the beneficial effect of iron-deficient diets and iron chelators. Rats with proteinuria have increased iron content in proximal tubular cells, and iron accumulation was the only independent predictor of both functional and structural damage [88]. Similarly, it has been shown that there is a substantial iron accumulation associated with increased cortical malondialdehyde in proximal tubular cells in the remnant kidney, suggesting reactive oxygen species generation. The sources of increased iron in the kidney have not been well delineated, but Alfrey et al. have suggested that urinary transferrin provides a potential source of iron [89,90].

Several studies have demonstrated an important role of iron in progressive kidney disease. It was reported that an iron-deficient diet (Fig. 8.1) or iron chelators prevent the development of tubulointerstitial disease and renal functional deterioration in nephrotoxic serum nephritis [90,91]. Remuzzi et al. have shown that rats fed an iron-deficient diet have a significant reduction in proteinuria and develop less glomerulosclerosis [92]. An iron chelator significantly reduces iron accumulation and tubular damage in the rat remnant kidney, a model for progressive renal disease [93].

Catalytic iron in human disease

A sufficient body of in vitro and in vivo information exists to postulate that catalytic iron is an important mediator in glomerular pathophysiology and progressive kidney disease. While the collective information on the role of oxidants and iron derived from models of glomerular disease as well as progressive renal failure is impressive, there is little information on the potential role of these mechanisms in human disease. There are many differences between animal models and glomerular disease in humans. For example, the animal model of minimal change disease is a toxic model, whereas the mechanism of minimal change disease in humans is not known. Similarly, the anti-Fx1A antibody, which is used for the animal model of membranous nephropathy, has been difficult to demonstrate in human membranous nephropathy. Indeed, the lessons from animal models of AKI have been disappointing when attempting to translate to human disease. We will summarize the limited information from human studies, which lend support that the mechanisms observed in animal models appear to be applicable to human disease.

Catalytic iron in diabetic nephropathy

Howard et al. have shown that urinary iron excretion is increased early in the course of diabetic kidney disease in humans [94]. We have compared labile iron in subjects with no renal disease or diabetes to patients with diabetes (Fig. 8.2A). Our data demonstrate that patients with overt diabetes have a marked increase in urinary catalytic iron. Similarly, patients with microalbuminuria have a marked and highly significant increase in urinary catalytic iron, indicating that urinary catalytic iron is not merely a reflection of albuminuria. Finally, some patients in the diabetic control group who do not have microalbuminuria have high catalytic iron, leading us to postulate that urinary catalytic iron precedes the onset of microalbuminuria and may predict patients at risk for diabetic nephropathy. Interestingly, recent studies have demonstrated that nontransferrin-bound iron levels are frequently increased in diabetes and have been implicated in a few studies with the vascular complications of diabetes [95].

We conducted a single-center, single-arm, open-label, proof-of-concept study to evaluate the safety and efficacy of the oral iron chelator deferiprone in reducing albuminuria in patients with diabetic nephropathy [96]. Adult patients with a diagnosis of diabetes mellitus and significant abnormal albumin excretion but with serum creatinine levels <1.2 mg/dL were included in this study. Patients received standard of care and enalapril, which was kept constant throughout the study. Deferiprone was administered in a daily dose of approximately 50 mg/kg in three divided doses for 9 months. The mean age of the 37 patients (21 males and 16 females) was 51.27 (±1.67) years. The blood glucose control measured by HbA1c was not significantly different between the baseline and final visit ($P = .68$). The mean albumin-to-creatinine ratio decreased with treatment of deferiprone as shown in

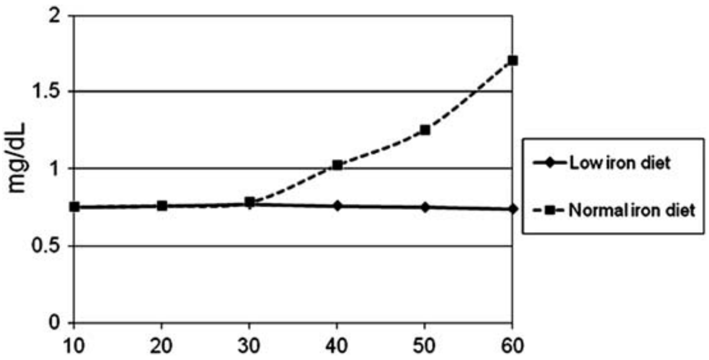


FIGURE 8.1 Effect of a low-iron diet in halting progression of kidney disease. Feeding a low-fat diet to rats with nephrotoxic serum nephritis prevented a rise in serum creatinine (vertical axis) over time course in days (horizontal axis) and provided histological protection (data not shown).

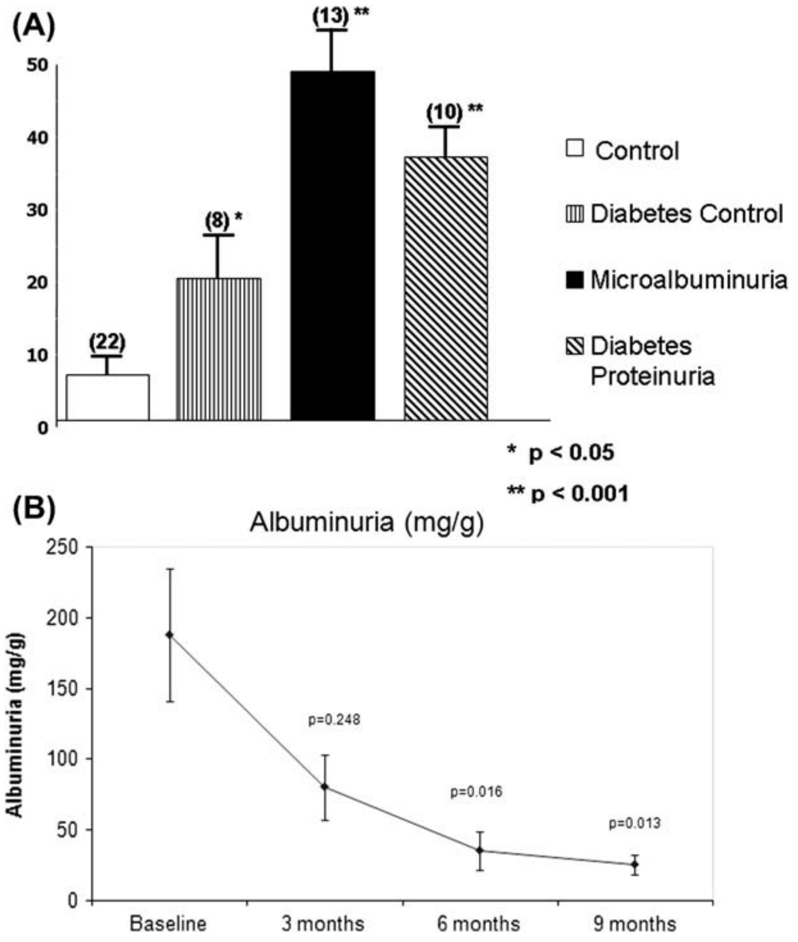


FIGURE 8.2 Urinary catalytic iron (nmols/L) in patients with diabetic nephropathy (A) and the effect of the iron chelator deferiprone on proteinuria (B).

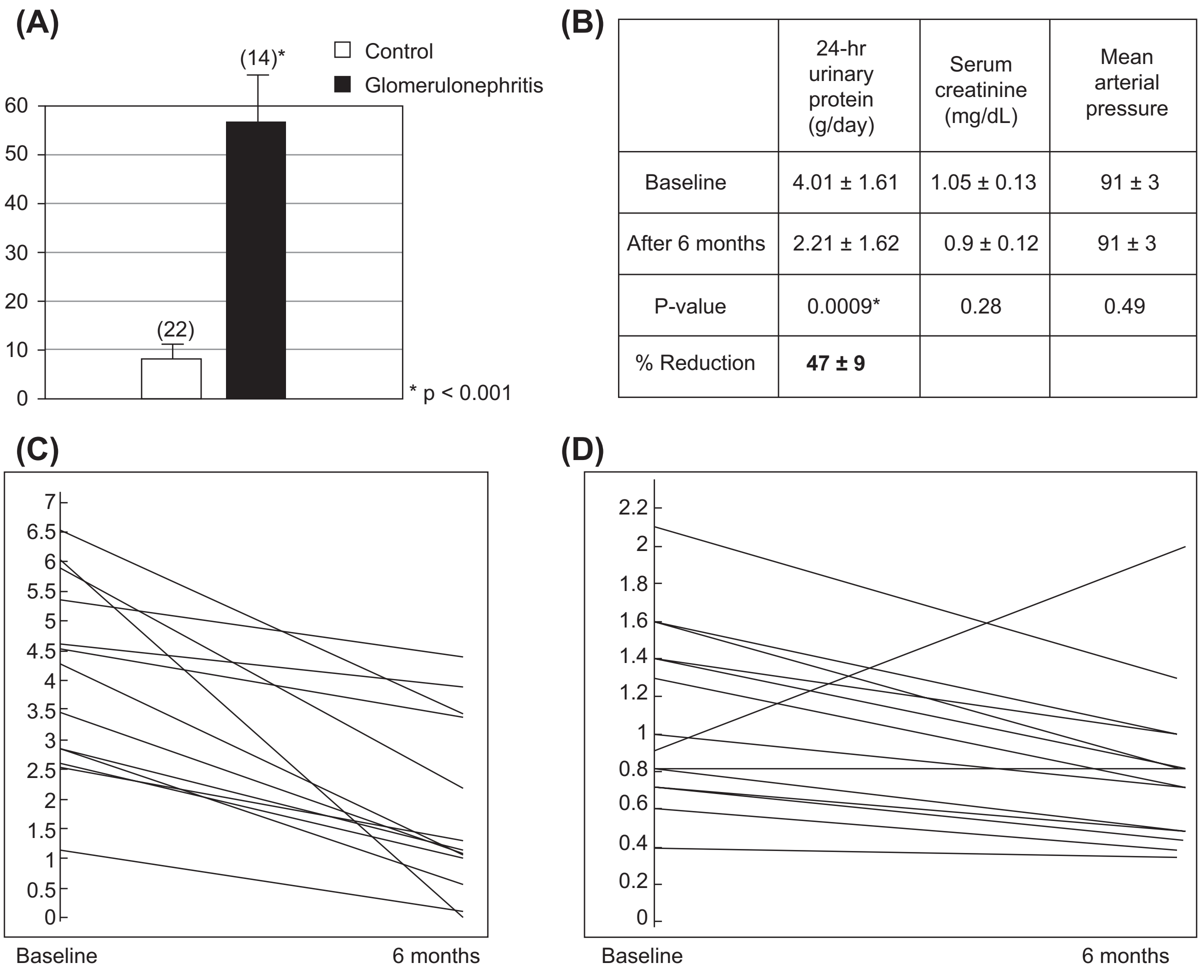
Fig. 8.2B. The serum creatinine levels remained stable throughout the course of the study. The calculated mean arterial blood pressure declined from a baseline value of 100.78 ± 1.7 to 97 ± 0.6 at 3 months ($P = .2$) but remained relatively stable from then on to 6 months (96.24 ± 0.7; $P = .6$) and 9 months. No clinically significant side effects were observed. Future randomized, double-blind trials, with careful monitoring of safety issues, may lead to the use of a new class of agents for the treatment of diabetic nephropathy.

Catalytic iron in chronic kidney disease

Nankivell et al. have reported increased iron content in patients with CKD [97]. Using the urinary catalytic iron assay described previously, we have shown a marked increase in patients who have biopsy-proven glomerulonephritis (Fig. 8.3A).

We conducted an open-label, proof-of-concept study in which patients with biopsy-proven glomerulonephritis were treated with deferiprone (50 mg/kg/day), and protein and serum creatinine were obtained 2–6 months after the administration of the iron chelator. As shown in Fig. 8.3B–D, treatment with the iron chelator significantly decreased the amount of total urinary protein in patients with glomerulonephritis [98]. Serum creatinine was 1.10 ± 0.15 before and 0.90 ± 0.10 ($n = 11$) at the end of the study period. Our data indicate an increase of catalytic iron in patients with glomerulonephritis and that treatment with an oral iron chelator leads to a reduction in proteinuria.

There is at least one published study in the literature in which the effect of a metal chelator on progressive kidney disease has been examined. Lin et al. have shown that chelation therapy with ethylenediaminetetraacetic acid (EDTA) in patients with chronic renal insufficiency results in a reduced rate of decline in the glomerular filtration rate (GFR) [99]. The authors attribute the beneficial effect to the chelation of lead, which also participates in the Fenton reaction. However, given the affinity constants for iron and lead, the large experimental evidence for the role of iron in kidney disease, and the demonstrated efficacy of EDTA in enhancing excretion of urinary iron, we believe that the beneficial effects are more likely to be explained by the chelation of iron rather than lead [100].



	24-hr urinary protein (g/day)	Serum creatinine (mg/dL)	Mean arterial pressure
Baseline	4.01 ± 1.61	1.05 ± 0.13	91 ± 3
After 6 months	2.21 ± 1.62	0.9 ± 0.12	91 ± 3
P-value	0.0009*	0.28	0.49
% Reduction	**47 ± 9**		

FIGURE 8.3 Urinary catalytic iron in patients with biopsy-proven glomerulonephritis (A); effect of deferiprone on urinary protein and serum creatinine in patients with steroid-resistant glomerulonephritis (B). Parts (C) and (D) depict individual patient data.

Concluding comments

One has to be cautious in extrapolating results from animal studies to humans. Unfortunately, all clinical trials in AKI based on animal models have failed. These include trials related to atrial natriuretic peptide [101,102], insulin-like growth factor [103,104], thyroxine [105,106], and furosemide [107,108]. Nonetheless, evidence that labile iron appears to be involved in a variety of models of AKI suggests that it may be a common mechanism of tissue injury. Additionally, the demonstration of an increase in labile iron in humans lends support to the possibility of similar pathophysiological mechanisms in humans. The availability of iron chelators with a favorable side-effect profile for short-term use makes them attractive for randomized clinical trials to evaluate their efficacy and safety in preventing or treating AKI.

There are several points from animal and human studies related to halting progression with a metal chelator that are worth noting. The observation that a reduction in proteinuria (provided it is not attributable to a fall in GFR) results in slowing progression of kidney disease has been reasonably well established, but only with ACE inhibitors and ARBs. This is in keeping with the data that albumin itself appears to have a significant effect on tubular cells, including enhanced the generation of oxidants and activation of the inflammatory response. However, it is conceivable for a therapeutic agent to preserve the tubulointerstitial region by abolishing the consequences of proteinuria or having a direct protective effect on the tubules. In diabetic and nondiabetic CKD, animal and human studies highlight the possibility of a beneficial effect without a reduction in proteinuria. A recent study demonstrated that bicarbonate supplementation slowed the rate of progression of renal failure to ESRD without reducing proteinuria [109]. In an open-label trial, pirfenidone was shown to slow the loss of kidney function in patients with focal segmental sclerosis with no reduction in proteinuria [110]. With a model of diabetic nephropathy, pirfenidone was reported to reduce the generation of reactive oxidant species and significantly reduce mesangial matrix expansion without affecting albuminuria. Alfrey and coworkers demonstrated that an iron-deficient diet or iron chelator provided both functional and histological protection against progression in a model of nephrotoxic serum kidney disease without affecting proteinuria [89,91]. Similarly, the study by Lin et al. showed EDTA provided protection against progression without reducing urinary protein [99]. Thus clinical studies targeted toward halting progression should focus not only on short-term studies on proteinuria, but also they would have to be of sufficient duration to evaluate the effect on renal function.

The evidence reviewed suggests the possibility of using iron chelators to halt the progression of kidney disease. The long-term use required for CKD makes oral iron chelators more attractive than parenteral medications. Currently, two oral iron chelators have been approved for human use in iron-overload states: deferasirox and deferiprone. Deferasirox has been shown to have some nephrotoxicity [111] but may nonetheless be potentially beneficial in patients with kidney disease. Deferiprone (1,2-dimethyl-3-hydroxypyridin-4-1, also known as L1) is the most extensively studied oral iron chelator and is approved for treatment of iron-overload states in Europe and India. In addition to its suitability for long-term treatment (because of oral administration), it has better tissue penetration compared to deferoxamine. The high-membrane permeability of deferiprone is well documented, as shown by its capacity to access and deplete intracellular iron pools [26]. In addition, a recent study has demonstrated its ability to remove labile iron from nuclei, endosomes, and mitochondria [26]. The major adverse effect reported so far in several thousand patients receiving deferiprone for periods of up to 14 years is transient agranulocytosis in 0.6% of patients. Based on the collective evidence to date, randomized, controlled, and double-blind trials may be warranted to evaluate the efficacy and safety of iron chelators to halt progression of CKD [112,113]. Targeting iron transport and hepcidin modulation may be effective alternative approaches to prevent and treat ferroptosis and kidney injury.

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C H A P T E R

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Carbonyl stress in uremia

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Introduction

Cardiovascular complications are important factors influencing the mortality of patients undergoing long-term dialysis treatment. Actual cardiovascular mortality in dialysis patients exceeds the expected mortality estimated on the basis of traditional risk factors, suggesting the existence of other unknown factor(s) that accelerate cardiovascular complications in uremic patients.

The accumulation in uremic circulation of uremic toxins or metabolites has been implicated in the development of atherosclerotic lesions in uremia. The field of uremic toxins has expanded markedly in the past. Most studies on uremic toxins have focused on disorders of enzymatic biochemistry. Attention has recently turned to progressive, nonenzymatic biochemistry. In this chapter, we focus on the carbonyl amine chemistry in uremia, which results in two types of irreversible alterations of proteins: advanced glycation through the Maillard reaction and advanced lipoxidation derived from lipid peroxidation. We discuss the chemistry of various reactive carbonyl compounds (RCOs) accumulating in the uremic circulation (carbonyl stress), their patho-biochemistry particularly in relation to atherosclerosis, and, finally, the contribution of nutrition to carbonyl stress.

Increased age and other protein modifications

In addition to the enzymatic glycosylation, a nonenzymatic process is initiated when proteins are exposed to glucose or other carbohydrates. For example, the glycosylated hemoglobin (hemoglobin A1c, HbA_{1c}) is formed in a nonenzymatic glycation pathway by hemoglobin's exposure to plasma glucose. This nonenzymatic process, called Maillard reaction, generates first reversible Schiff base adducts, subsequently more stable Amadori rearrangement products, and, eventually, the irreversible advanced glycation end products (AGEs) [1]. The role of AGEs in human pathology was initially highlighted in diabetes with hyperglycemia: AGEs levels are correlated with those of fructose-lysine [2], a surrogate marker of prevailing plasma glucose concentration, and also with the severity of diabetic complications [3], a finding supporting their clinical relevance.

Of note, AGEs accumulate in uremic patients to a much greater extent than in diabetics. Plasma levels of two well-known AGEs, pentosidine [4] and carboxymethyl-lysine (CML) [5], in hemodialysis patients by far exceed those in normal or diabetic subjects. Other AGE adducts also accumulate in uremia such as glyoxal-lysine dimer, methylglyoxal-lysine dimer, and imidazolone [6,7]. Among dialysis patients, diabetics and nondiabetics had similar plasma pentosidine and CML levels [4,5]. Neither pentosidine nor CML correlated with fructose-lysine levels in uremic subjects. It became thus clear that factor(s) other than hyperglycemia are critical for AGE accumulation in uremia. The fact that over 90% of plasma pentosidine and CML are bound to albumin [4,5] suggests that its accumulation does not simply result from a decreased renal clearance of AGE-modified proteins.

The second approach to irreversible protein modification in uremia derives from studies of lipid metabolism, especially lipid peroxidation. Proteins are modified not only by carbohydrates but also by lipids. For instance, proteins modified by malondialdehyde accumulate in plasma

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proteins of hemodialysis patients [5]. Malondialdehyde as well as other lipid peroxidation product-modified proteins are called the advanced lipoxidation end products (ALEs) [8].

Uremia is thus characterized by irreversible nonenzymatic protein modifications by AGEs/ALEs. In renal failure patients, lipid peroxidation and advanced glycation of plasma proteins or skin collagens increase in close relation to each other [5,9].

Carbonyl stress

Both AGEs and ALEs are formed by carbonyl amine chemistry between protein amino residues and RCOs [8]. These RCOs are constantly produced during the metabolism of carbohydrates, lipids, and amino acids [10–12]. Recent studies confirm the accumulation of various RCOs derived from both carbohydrates and lipids in uremic plasma and suggest that they are indeed precursors of AGEs and ALEs [8,13,14]. The prevailing plasma pentosidine level, for example, is shown to mirror the level of its RCOs precursor [13]. The accumulation in uremic plasma of various RCOs derived from either carbohydrates or lipids as well as the subsequent carbonyl modification of proteins suggest that chronic uremia may be characterized as a state of "carbonyl stress" [14] (Fig. 9.1). AGEs/ALEs are, therefore, not markers of hyperglycemia/hyperlipemia in uremia but represent carbonyl stress and RCO accumulation.

Two competing, but not mutually exclusive, hypotheses are considered to account for the cause of carbonyl stress [14]: an increased generation or a decreased detoxification of RCOs. First, the production of RCOs is increased by oxidative stress. Several reports point to the existence of an increased oxidative stress in uremia [15]. The uremic oxidative stress is further worsened during hemodialysis treatment, that is, activation of complement and neutrophils and generation of reactive oxygen species. A causal role of the oxidative stress in AGE and ALE formation is supported by the correlation existing in uremic serum between pentosidine and oxidative markers, such as dehydroascorbate (oxidized ascorbate) [16] and advanced oxidation protein products [17].

However, recent studies have shown that several RCOs derived from nonoxidative chemistry are also raised in uremia, suggesting the simultaneous involvement of nonoxidative chemistry in the genesis of uremic carbonyl stress. For example, the levels of 3-deoxyglucosone [18] and methylglyoxal [19], and of their protein adducts, all of which are formed independently from oxidative reactions, are increased in plasma proteins of hemodialysis patients. Carbonyl

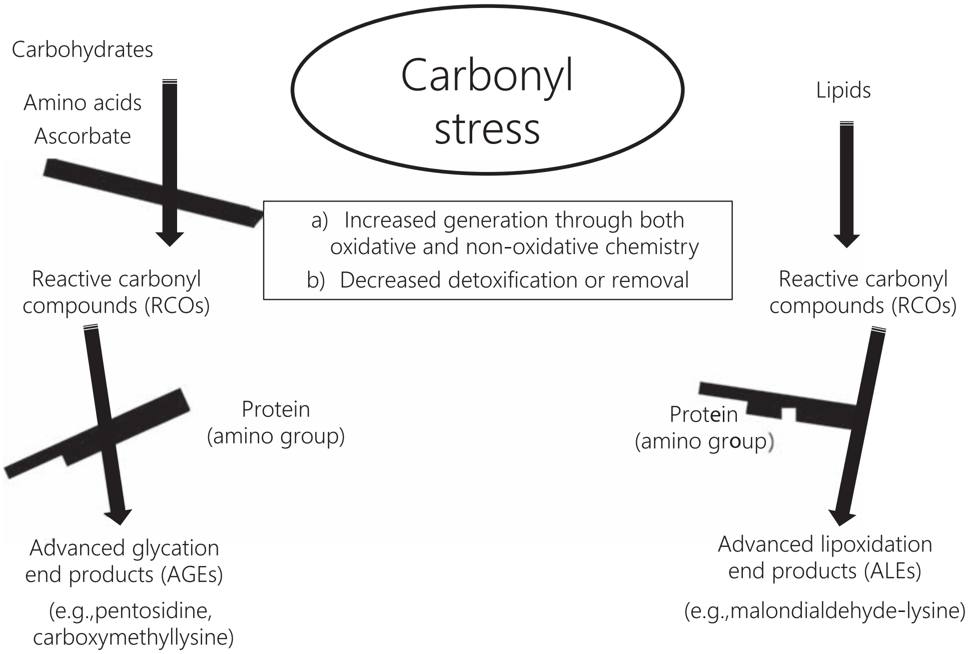
Carbohydrates
Amino acids
Ascorbate
Carbonyl stress
Lipids
a) Increased generation through both oxidative and non-oxidative chemistry
b) Decreased detoxification or removal
Reactive carbonyl compounds (RCOs)
Reactive carbonyl compounds (RCOs)
Protein (amino group)
Protein (amino group)
Advanced glycation end products (AGEs)
(e.g.,pentosidine, carboxymethyllysine)
Advanced lipoxidation end products (ALEs)
(e.g.,malondialdehyde-lysine)

FIGURE 9.1 Carbonyl stress generated in uremia during the metabolism of carbohydrates, lipid, and amino acids. Both AGEs and ALEs are formed by the carbonyl amine chemistry between protein amino residues and RCOs, which are constantly produced in uremia during the metabolism of carbohydrates, lipids, and amino acids either by an increased generation of RCOs through both oxidative and nonoxidative chemistry or by a decreased detoxification or removal of RCOs. *AGEs*, Advanced glycation end products; *ALEs*, advanced lipoxidation end products; *RCOs*, reactive carbonyl compounds.

stress thus represents much broader derangement in the nonenzymatic biochemistry of both oxidative and nonoxidative reactions.

The alternative hypothesis is therefore proposed: the RCOs rise in uremia is derived from a decreased removal of RCOs. RCOs are detoxified by several enzymatic pathways, such as the glyoxalase pathway [20]. Reduced glutathione (GSH) and nicotinamide adenine dinucleotide phosphate (NAD(P)H) contribute to their activity. RCOs such as methylglyoxal and glyoxal react reversibly with the thiol group of glutathione and are subsequently detoxified by glyoxalases I and II into D-lactate and glutathione. NAD(P)H also replenishes glutathione by increasing the activity of glutathione reductase. Decreased levels of glutathione and NAD(P)H can, therefore, result in augmented levels of a wide range of RCOs. It is of interest to know in this context that the glutathione concentration in red blood cells and the serum activity of glutathione-dependent enzymes are significantly reduced in uremia [21].

There has been little evidence that the RCO detoxification mechanism might influence in vivo RCO formation and, therefore, serum AGE levels. Of note, a patient on hemodialysis has been identified, in whom a deficiency of glyoxalase I was associated with unusually elevated levels of AGEs (pentosidine and CML) and of their precursors [22]. This patient had suffered from recurrent cardiovascular complications despite the absence of significant risk factors. Subsequently, genetic defects of the glyoxalase I have been identified in a subpopulation of schizophrenic patients [23]. Despite normal renal function and normoglycemia, these patients are associated with strikingly elevated levels of AGEs, implicating the glyoxalase detoxification system in the actual level of AGEs in vivo.

A mechanism that regulates carbonyl stress is another issue of interest. Superoxide dismutase (SOD) and glutathione peroxidase are antioxidant enzymes involved in the metabolism of hydrogen peroxide, which accelerates carbonyl stress [12,24]. It is of note that glutathione peroxidase activities correlated inversely with pentosidine levels in uremic plasma [21]. On the other hand, the plasma extracellular SOD levels correlated with the pentosidine levels. These data suggest a link of altered redox regulation by antioxidant enzymes to an increased carbonyl stress. Furthermore, recent observation gives a new perspective in the regulation of AGE production by linking it to the prevailing effect of nitric oxide (NO) [25]: NO effectively inhibits the pentosidine generation in vitro. It is best explained by the ability of NO to scavenge carbon-centered radicals and hydroxyl radicals and, consequently, to suppress the formation of RCOs and pentosidine. NO might be therefore implicated in the atherogenic and inflammatory effects of carbonyl stress.

Clinical consequences of carbonyl stress

It remains to be demonstrated whether carbonyl stress is the passive result of long-term accumulation of vascular protein modifications or, alternatively, it plays an active role in the pathogenesis of atherosclerosis. Studies support the active contribution of carbonyl stress in the atherogenesis.

The levels of AGEs in arterial tissues are higher in dialysis patients than in normal subjects [26]. Both AGEs/ALEs are detectable by means of immunohistochemical approaches in the fatty streaks and in the thickened neointima of uremic patients [27]. Available evidence suggests that plasma levels of pentosidine are an independent variable of the presence of ischemic heart diseases and hypertension [28], and of left ventricular wall thickness measured by echocardiography in hemodialysis patients [29]. Skin accumulation of AGEs using the autofluorescence reader, a recently developed noninvasive device, showed that the AGE accumulation is an important predictor for arterial stiffening in ESRD subjects [30].

In vitro, AGE- and ALE-modified proteins initiate a range of cellular responses [31–35], including stimulation of monocyte chemotaxis and apoptosis, secretion of inflammatory cytokines from macrophages, proliferation of vascular smooth muscle cells, stimulation of platelet aggregation, and of vascular endothelial growth factor (VEGF) production from endothelial cells. Independently of their AGE- and ALE-mediated effects, RCOs also interfere with various cellular functions and induce not only structural but also functional alterations of proteins. For example, exposure in vitro of cultured mesothelial and endothelial cells to methylglyoxal increases mRNA and protein synthesis of VEGF [36]. Repeated intraperitoneal loads of methylglyoxal, given to rats, also increase in vivo the peritoneal membrane expression of VEGF [36]. Noteworthy in this context is the demonstration that, both in long-term peritoneal dialysis patients and in chronic uremic rat model [36,37], an increasing staining for AGEs, CML, and pentosidine is detected in peritoneal arterial walls, together with an augmented VEGF and basic fibroblast growth factor (FGF2) expression.

There are two major pathways, direct and indirect, through which carbonyl stress is sensed by cells and triggers a cascade of intracellular signal transduction. In the indirect pathway the RCOs first interact with proteins or lipids in the physiological environment surrounding the cells, which then undergo nonenzymatic glycation and lipoxidation resulting in the production of AGEs and

ALEs. They bind with the receptor(s) on cell surfaces, for example, RAGE, thereby initiating intracellular signal transduction [38]. By contrast, the direct pathway works before generation of AGEs and ALEs. The RCOs directly attack target molecules on cell surfaces or inside the cells, which initiate the subsequent signal transduction [39–43]. For example, glyoxal and methylglyoxal possess two reactive carbonyl groups to make protein aggregates by cross-linking, which may amplify the signals for tyrosine phosphorylation of cellular proteins [39]. In another model the binding of 4-hydroxynonenal, an RCO generated during lipid peroxidation, with epidermal growth factor receptor induces its clustering on the cell surface, thereby activating the mitogen-activated protein family kinases [40].

In vascular lesions an increased oxidative stress, together with altered redox regulation and decreased RCO detoxification, may increase carbonyl stress, exacerbate endothelial dysfunction, and, eventually, lead to the development of atherosclerosis.

The consequences of carbonyl stress have also been implicated in other complications associated with uremia or long-term dialysis. First, renal failure is associated with resistance to the action of calcitriol (1,25-dihydroxyvitamin D) [44], which is partly attributed to the inhibition by unknown uremic toxins of the interaction between the vitamin D receptor and vitamin D response elements [45]. Patel and coworkers [46] demonstrated that RCOs capable of Schiff base formation with lysine residues of the vitamin D receptor inhibit its interaction with the vitamin D response element. Second, dialysis-related amyloidosis is a serious bone and joint destruction associated with uremia [47]. Immunohistochemical and chemical analyses have indicated that β2-microglobulin amyloid deposits are modified by carbonyl stress [48–50]. Third, the major problem associated with long-term peritoneal dialysis is the progressive deterioration of the peritoneal membrane structure and function, that is, ultrafiltration failure, which curtails its use in approximately 50% of patients within 5 years [51]. Recent studies have cast a new light on its molecular mechanism [52]. During peritoneal dialysis, RCOs resulting both from glucose PD fluid and from uremic circulation enter the peritoneum [14], modify the peritoneal membrane [53], and initiate a number of cellular responses, leading to angiogenesis and vasodilation. The latter may increase the permeability for small solutes and glucose, stimulate glucose reabsorption, and result in faster than normal dissipation of the osmotic gradient across the peritoneal membrane with an eventual loss of ultrafiltration [52].

Nutrition and carbonyl stress

The advanced glycation of proteins has been initially unraveled by food and nutrition biochemists. Various kinds of food indeed contain a significant amount of CML and pentosidine [54,55]. Previous studies demonstrated that although the modification of proteins with AGEs reduces the digestibility of proteins either by gaining resistance to the enzymatic digestion of proteases or by inhibiting digestive enzyme activity [55], a significant proportion of dietary AGEs are absorbed by the gastrointestinal tract into the circulation [56,57]. He et al. demonstrated that ~10% of ingested AGE-modified ovalbumin was absorbed into the rat circulation [57]. Of particular interest is the demonstration of a relationship between renal function and exogenous or food-derived AGE levels in the serum [56]. Synthesized pentosidine was given orally to both normal and uremic rats, and their kinetics in the circulation was investigated. In normal rats, plasma pentosidine rose slightly and transiently to become undetectable at 6 hours. By contrast, in rats with 6/7 nephrectomy, plasma pentosidine peaked at 3 hours and fell thereafter (calculated biological half-life of 4.08 ± 1.68 hours). In bilaterally nephrectomized rats, plasma pentosidine level peaked at 12 hours and decreased subsequently (calculated biological half-life of 47.3 ± 10.2 hours). The pathological contribution of exogenous or food-derived AGEs still remains unknown.

Several lines of evidence have implicated the dietary contribution to the in vivo AGE accumulation. Dietary calorie restriction reduces the accumulation of tissue AGEs without affecting the survival of the animals [58,59]. Of note is the recent report by Sell et al. that longitudinal determination of the rates of pentosidine and CML formation predicts the individual longevity in mice, and that calorie restriction retards this rate as compared to ad libitum feeding [60]. Recent study by Uribarri et al. demonstrated that dietary AGEs contribute significantly to the elevated plasma AGE levels in uremic patients [61]. More studies are required to elucidate the contribution of nutrition to the pathophysiology of carbonyl stress and to the eventual cardiovascular-associated mortality.

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CHAPTER

10

Metabolic and nutritional responses to acidemia and alkalemia

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Introduction

Clinical textbooks of nephrology often focus on the disturbances that alter hydrogen ion accumulation in the blood (acidosis or alkalosis) independent of the final blood pH. After all, the prompt recognition of an underlying disorder aids differential diagnosis and allows rapid intervention in many life-threatening disorders. Respiratory acidosis and alkalosis result from alterations in levels of carbon dioxide (CO_2) while alterations in dietary intake as well as renal, digestive, and endocrine disorders result in alterations in noncarbonic or metabolic acid [1]. However, there are consequences when the body fails to tightly regulate blood pH at 7.40 regardless of the cause of the disorder [2]. A blood pH below 7.40 is defined as acidemia and above 7.40 is defined as alkalemia. In chronic disease the accumulation of metabolic acid or base in the body can profoundly affect long-term outcomes via effects on mineral and protein metabolism. These consequences have been best studied in models of chronic kidney disease (CKD). There is much less information about effects of acidemia in the general population and even less information about the sequela of respiratory acid and base disorders. All of the acute and many of the chronic mechanisms in response to metabolic acidosis should apply to respiratory acidosis, but there are known differences between the responses to respiratory and metabolic acidosis that have not been fully characterized.

Loss of lean body mass and bone mineral are hallmarks of metabolic acidemia in CKD, and epidemiologic data suggest that these losses correlate strongly with outcomes in patients with CKD and end-stage renal disease (ESRD) [3,4]. In addition to effects on all-cause mortality, other responses to acidemia also appear to drive loss of renal function in patients with CKD [5]. Responses to mild chronic alkalemia, on the other hand, seem to ameliorate catabolism, but more severe alkalemia can be associated with specific acute and chronic complications primarily involving mineral metabolism. Our focus is largely on the nutritional consequences: anabolic and catabolic effects on bone and muscle, the benefits and risks of correction of acidemia on protein and bone metabolism, and the effects of high or low dietary acid loads. While the focus of this chapter is on patients with kidney disease with acidemia, we also review the evidence of the effects of acidemia and high dietary net acid load in the general population. The role of alkali compounds or of a diet providing a low net acid load or an alkaline (plant food) load for slowing progression of CKD is discussed in Chapter 19, Alkalization to Retard Progression of Chronic Kidney Disease.

Responses to acute acidemia and alkalemia

The acute response to an acid load, such as metabolic acid from a typical Western diet or increasing respiratory acid from lowering ventilation, involves buffering by the bicarbonate–carbon dioxide system, protein anions, and bone [6]. Accepting hydrogen ions to the carboxylic side chain of proteins in acute acidosis alters the charge of these side chains and leads to changes in the function, binding, folding, and stability of enzymes, receptors, and transport proteins. This leads to the characteristic acute physiological responses seen in metabolic acidemia such as changes

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in the respiratory rate, carbon dioxide−bicarbonate system, and bone buffering.

The body readily tolerates acute metabolic acidemia [7,8]. For example, the blood pH may fall below 7.2 during strenuous exercise without immediate adverse effects. In some ways, acute acidemia in the pH range of 7.2−7.4 helps the body during exercise or acute illness; cardiac index generally rises as catecholamine release is mildly stimulated by central sensing mechanisms and by increased vasodilation [7]. Increased tissue oxygen delivery occurs via this rise in cardiac index, the Bohr effect (shifting oxygen from hemoglobin to tissues), and stimulation of the respiratory drive [9]. Both innate- and cell-mediated immunities are increased in acidemia resulting in an increased ability to fight infection [10]. The liver shifts from making albumin to making acute-phase proteins of innate immunity. Endothelial and immune cell production of inflammatory chemokines and cytokines increases, as does neutrophil activation and hydrogen peroxide production.

However, studies show numerous defects in immune function when pH is below 6.9, and the responses to infection may be severely compromised [11,12]. As reviewed later, an acid pH above 7.0 seems to improve certain aspects of immune function. For example, cytokine release from macrophages in response to nitric oxide is stimulated by a fall in pH from 7.4 to 7.0, while a pH of 6.5 suppresses it [11]. The cardiovascular consequences of a more severe acute acidosis are clear in animal studies [8]. Part of the vasodilator response to acidosis is due to reduced effectiveness of catecholamine receptor signaling [13]. Below a pH of 7.1, the development of catecholamine resistance exceeds the effects of the elevation in plasma catecholamines, and cardiac index falls. The incidence of cardiac arrhythmias also rises with severe acidemia, and these effects are pronounced below a pH of 6.9 [14]. Because of the potential benefits of less severe acidemia on the circulation, recent critical care guidelines do not recommend alkali therapy for correction of acidemia (to improve hemodynamics) in patients with shock and lactic acidosis where arterial blood gas pH is 7.15 or higher [15]. In extremely strenuous competitive sports, there is concern about the adverse effects on exercise performance if the pH falls too low. Indeed, supplementation with alkali immediately before exercise appears to improve athletic performance in sports activities that induce severe lactic acidosis [16].

In contrast, acute metabolic alkalemia appears to be dangerous in the acutely ill medical or surgical patient, and the risk of death rises with increasing blood pH [17,18]. Because metabolic alkalosis is often sustained by life-threatening conditions (e.g., heart failure, volume depletion), it is not clear to what extent the increase in mortality is due to the acute alkalosis itself or to the underlying conditions causing the alkalosis. Metabolic alkalosis decreases tissue oxygen delivery via vasoconstriction and the Bohr effect. Decreased oxygen delivery may also contribute to decreased cerebral blood flow resulting in lethargy, confusion, and worsening heart failure. In severe cases, coma and seizures may result. The respiratory center can be depressed, and alveolar ventilation decreased. However, the most feared complications of acute alkalemia are due to the lowering of ionized calcium levels as a consequence of increased albumin binding [19]. Neuromuscular irritability, which is manifested by muscle twitching, spasm, and tetany, is associated with alkalemia and is most likely calcium related. An alkaline pH has been shown to decrease aldosterone release in response to angiotensin II, resulting in vasodilation and decreased blood pressure. Myocardial contractility is blunted, as is the inotropic response to norepinephrine. As with severe acidemia, arrhythmias also increase. When the pH is greater than 7.75, the fall in ionized calcium is life-threatening, especially if hypokalemia is present; cardiac arrest commonly results. These hazards of acute alkalemia underscore the need for caution when acutely correcting acidemia. For example, an increased incidence of sudden death has been reported in hemodialysis patients when using dialysate containing higher concentrations of bicarbonate [20]. While hypokalemia may contribute to this adverse outcome, studies provide some evidence that two consequences of alkalemia, the suppression of respiration and an increase in arrhythmias, may also be involved [20,21].

Bone buffering and calcium homeostasis in chronic acidemia

After the initial buffering of acids by the bicarbonate system, bone and protein serve as buffers for excess acids (Table 10.1). Calcium carbonate and phosphate in the bone matrix buffer acids (hydrogen ion; i.e., protons) to maintain the blood pH [22]; this results in the release of calcium, sodium, potassium, and phosphate ions from bone [23]. In respiratory acidosis the high carbonate concentration in blood (derived from CO_2) prevents bone resorption. Metabolic acidosis also stimulates bone-absorbing osteoclasts and suppresses bone-forming osteoblasts. Acidemia has been shown in vitro to increase the activity of osteoblastic and osteoclastic genes. Proton-sensing proteins appear to play a role in this response. For example, in mice, the ovarian cancer G protein−coupled receptor, OGR-1, responds to acidemia by regulating the differentiation, metabolism, and

TABLE 10.1 Effects of chronic metabolic acidosis on bone and on protein metabolism.

1. Dissolution of bone
    - a. Direct effect of acid on bone mineral content
    - b. Increased osteoclast and decreased osteoblast activity
    - c. Increased plasma glucocorticoids
    - d. Increased serum parathyroid hormone (clinically apparent in uremia only)
    - e. Decreased plasma insulin-like growth factor-I
2. Hypercalciuria and hyperphosphaturia leading to phosphate and calcium wasting
    - a. Increased filtered load of calcium and phosphorous
    - b. Decreased tubular reabsorption of calcium and phosphorous
3. Protein malnutrition and muscle wasting
    - a. Activation of muscle proteolysis via caspase-3 and the ubiquitin–proteasome proteolytic system
        - i. Direct effect of pH
        - ii. Increased plasma glucocorticoids
        - iii. Insulin resistance in nonhepatic organs
    - b. Activation of branched-chain ketoacid dehydrogenase
        - i. Direct effect of pH
        - ii. Increased plasma glucocorticoids
    - c. Increased hepatic glutamine synthesis and renal glutamine extraction
    - d. Decreased muscle protein synthesis
        - i. Direct effect of pH
        - ii. Insulin resistance in nonhepatic organs

pH homeostasis in both osteoblasts and osteoclasts [24]. Through these proton-sensing proteins, acidemia leads to increased expression of cyclooxygenase mRNA, mRNA of the osteoclast activator, and receptor activator of nuclear factor-κB ligand [23]. These processes, coupled with direct inhibition of osteoid mineralization and hormonal changes (discussed later), lead to bone disease with features of osteoporosis and osteomalacia [23]. This direct effect of metabolic acidosis on bone demineralization appears to occur by different mechanisms than those induced by increased cortisol and parathyroid hormone (PTH) or decreased insulin-like growth factor-I (IGF-I) and is additive to those effects. For example, parathyroidectomy does not block the effect of metabolic acidosis on bone [25].

When renal function is normal or near normal, mobilization of calcium from bone in response to metabolic acidosis leads to hypercalciuria. The degree of hypercalciuria is directly proportional to the acid load [23]. If serum calcium rises as a result of the mobilization of bone calcium due to the acidemia, the amount of calcium filtered at the glomerulus increases. But the major effect of acidemia on renal calcium handling is a direct inhibition of tubular calcium reabsorption [26]. However, the increase in urinary calcium in metabolic acidosis occurs independently of the level of filtered calcium [27]. Respiratory acidosis causes a smaller increase in urinary calcium excretion, presumably because there is less calcium efflux from bone. Thus chronic acidemia, especially metabolic acidosis, contributes directly to negative calcium balance by causing dissolution of bone and by raising renal calcium losses.

Increased ammoniagenesis and muscle wasting in acidemia

Acidemia directly stimulates hepatic glutamine production, which is required for renal ammoniagenesis and renal acid excretion. By accelerating muscle protein degradation, metabolic acidosis leads to release of amino acids that are used to synthesize glutamine in the liver [28]. Moreover, acidemia increases the oxidation of branched-chain amino acids (BCAA) in muscle, which provides much of the nitrogen used in the hepatic synthesis of glutamine [29]. The evidence for this latter response is that metabolic acidosis activates the rate-limiting enzyme for the irreversible decarboxylation of BCAA, branched-chain ketoacid dehydrogenase (BCKAD) in muscle, and this response accounts for BCAA degradation [29]. Plasma levels of BCAA in uremic rats are low compared to pair-fed, control rats, and these low levels are linked to increased oxidation in muscle [30]. The influence of acidosis in initiating and maintaining these processes was proven by demonstrating that adding $NaHCO_3$ to the diet to correct the metabolic acidosis of chronic uremia restored to normal both plasma levels of BCAA and the rates of amino acid oxidation in muscle [30]. People also exhibit activation of muscle BCKAD activity in response to acidemia. Studies of normal adults confirm that an acid diet results in a 25% stimulation of BCAA decarboxylation [31].

To provide the BCAA for ammoniagenesis, acidemia provokes negative muscle protein balance by direct and indirect responses. The direct effect is seen by lowering the pH in the media of cultured myocytes, which results in a slight decrease in protein synthesis coupled with a larger increase in protein degradation. This is consistent with a direct effect of acidemia on protein metabolism [32,33]. Correction of acidemia by inducing respiratory alkalosis reverses these effects on protein metabolism [34]. In uremic rats, there must also be an indirect effect, because the measured pH in muscle is normal in vivo in both the resting state and in the recovery from acidification [35]. This suggests that factors other than acidemia must act as signals to increase protein degradation. One of these factors is glucocorticoids that are known to be released with acidosis and to directly induce protein catabolism [28,36]. This was tested in rats where it was found that adrenalectomy blocks the effects that acidosis induces on protein and amino acid catabolism, but adding a physiologic amount of glucocorticoids restores the catabolic effect of acidosis, in vivo [37]. Both acidosis and glucocorticoids are also required to increase the activity of BCKAD and of the ubiquitin–proteasome proteolytic system in muscle and cultured myocytes [33] (see later).

The ATP-mediated ubiquitin–proteasome pathway plays an important role in muscle degradation. In the ubiquitin–proteasome pathway, proteins are targeted for degradation by ATP-dependent conjugation of a protein to ubiquitin, a small protein found in all cells. Protein–ubiquitin conjugates are degraded in another ATP-dependent process by the 26S proteasome, a large multicatalytic, multiple subunit proteolytic complex, found in the nucleus and cytoplasm of all cells [38]. Experiments using adrenalectomized rat models, which have an absence of glucocorticoids, demonstrated that activation of the ubiquitin–proteasome pathway in acidosis requires glucocorticoids. Interestingly, neither glucocorticoid excess nor acidosis alone was sufficient to activate the ubiquitin–protein pathway; both processes are required [28,39]. Further, the response to acidosis occurs at a transcriptional level. A rise in mRNAs encoding ubiquitin and subunits of the proteasome in muscle of acidotic rats with chronic uremia and acidosis has been demonstrated [40]. In studies of cultured muscle cells and isolated muscles, metabolic acidosis increased the expression of ubiquitin mRNA and mRNA encoding the subunits of the proteasome [41]. Respiratory acidosis also upregulates the ubiquitin/proteasome system in skeletal muscle, although it is not clear if the lower pH or the increased carbon dioxide is the major driver of this response [42].

Furthermore, abnormalities in insulin and IGF-I signaling activate muscle protein degradation in the ubiquitin/proteasome system and caspase-3, a protease that disrupts the complex structure of muscle proteins to provide substrates for the ubiquitin/proteasome system (Fig. 10.1) [41,43,44,102]. Both acidemia and glucocorticoids block intracellular signaling induced by the insulin/IGF-I receptor, but by slightly different mechanisms [44,45]. Glucocorticoids reduce insulin receptor substrate-1 phosphorylation, while acidemia has a greater effect on recruitment of the phosphoinositide 3-kinase p85 subunit to prevent downstream signaling. There is strong evidence that both glucocorticoids and a second signal that induces insulin resistance are required for muscle atrophy [46]. These signaling pathways regulate two major proteolytic systems responsible for muscle atrophy: ubiquitin/proteasome and caspase-3. The cleavage of muscle proteins by caspase-3 is a preliminary step required for muscle proteins to be digested by the ubiquitin–proteasome system [47]. Supporting this model, insulin and IGF-I suppress protein degradation in the body and insulin resistance occurs with acidemia [48,49]. The effect of acidosis to impair insulin signaling may also contribute to the small, variable decrease in muscle protein synthesis seen in acidemia [50].

Acidemia is not the sole factor driving muscle wasting in kidney disease through these pathways. For example, rats with insulin-dependent diabetes, exposed to inflammatory cytokines or treated with uremic toxins also exhibit increased muscle proteolysis via the ubiquitin–proteasome system [51]. Acidemia, diabetes, inflammatory cytokines, and other uremic toxins all induce insulin resistance. Correction of acidemia in chronically uremic rats measurably improves muscle protein degradation but does not restore it to normal levels. In contrast, the impairment of protein synthesis in uremic rats persists after correction of metabolic acidemia [36,40]. Acidemia shows synergy with other mediators of uremic muscle wasting, and the catabolic effects of acidemia appear to increase with declining renal function.

Mechanisms of the synergy between acidemia and other uremic signals on muscle protein metabolism go beyond impaired insulin and IGF-I signaling. For example, inflammation activates muscle proteolysis via the ubiquitin–proteasome system in part through myostatin, a member of the TGF-β superfamily of secreted proteins. Myostatin, produced in skeletal muscle, acts as a powerful negative regulator of muscle mass through the type IIB activin receptor. Inflammatory cytokines and glucocorticoids increase myostatin production in skeletal muscle via the signal transducers and activators of transcription 2 and 3 (STAT 2/3) signaling [52,53]. Under the influence of interleukin (IL)-6, STAT 2/3 localize in the nucleus and bind to transcription factors driving transcription of myostatin. Blocking STAT 2/3, myostatin or their signaling in CKD reduces muscle wasting in mice. Acidemia, by itself, does not appear to be a regulator

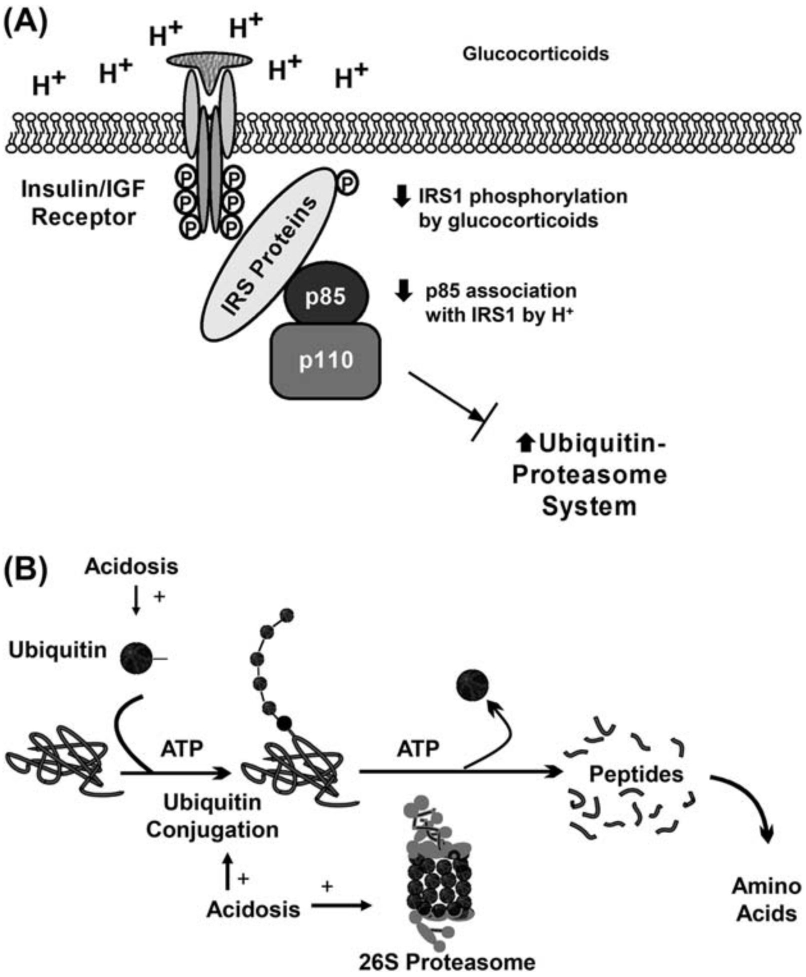

FIGURE 10.1 (A) Acidemia and glucocorticoids block insulin and/or IGF-I signaling to activate the ubiquitin–proteasome system in muscle. Signaling through the insulin or IGF-I receptors normally prevents muscle wasting. Acidemia and glucocorticoids work synergistically to impair signaling through the insulin receptor after binding of insulin or IGF-I. Glucocorticoids partially reduce the phosphorylation of insulin receptor substrate-1 induced by insulin binding, while acidosis blocks recruitment of the phosphoinositide 3-kinase p85 subunit to prevent downstream signaling. Impairing signaling allows the activation of the ubiquitin–proteasome system. (B) Acidosis stimulates the ubiquitin–proteasome system by affecting multiple steps. Proteins freed from the muscle fibers by caspase-3 are conjugated by ubiquitin, and the ubiquitin targets them to the proteasome where they are destroyed. Acidosis increases the amount of ubiquitin and proteasomes and also increases the conjugation of protein with ubiquitin. *IGF-I*, Insulin-like growth factor-I.

of the myostatin or STAT 2/3 pathways but increases serum glucocorticoids and IL-6 (see later). Thus acidemia would be expected to have synergy with other uremic toxins that also increase these mediators. To summarize, abundant evidence from experimental models and human studies demonstrates that metabolic acidemia accelerates irreversible oxidation of BCAA and degradation of skeletal muscle protein. However, the catabolic effect is much greater in the presence of other disturbances that also drive muscle wasting, especially those that increase glucocorticoids and inflammation.

Hypoalbuminemia, inflammation, and innate- and cell-mediated immunities

Since catabolism is an important part of the response to infection, it is not surprising that acidosis plays a role in activating immunity. Metabolic acidosis appears to have direct and indirect effects in suppressing albumin synthesis and activating the innate immunity via the acute-phase response in the liver (see also next paragraph). When metabolic acidosis was induced in healthy volunteers through the ingestion of ammonium chloride, there was a significant decline in the synthesis rate of albumin as well as in serum albumin levels [54]. Consistent with these findings, serum albumin and prealbumin levels increased significantly in a group of elderly patients who were given enough alkali to maintain serum bicarbonate levels at 24 mM [55]. Similar results were seen in randomized studies of patients with stage 4 CKD [56], but it has been harder to demonstrate these same results in ESRD patients. Correction of metabolic acidosis with alkali has been shown to improve serum albumin levels in some ESRD studies [57], but not in others [58]. When metabolic acidosis was corrected in patients on hemodialysis with and without inflammation, as measured by C-reactive protein (CRP), there was a reduction in protein catabolism, as measured by normalized protein nitrogen appearance (nPCR/nPNA) in both groups [59]. However, the serum albumin levels rose only in those patients with low inflammatory markers, as measured by CRP. Taken together, these studies suggest that acidemia enhances the switch from albumin synthesis to synthesis of acute-phase response proteins in the liver, but other inflammatory signals can override correction of acidemia.

Acidemia also contributes to inflammation that reduces albumin synthesis and increases innate- and cell-mediated immunities [10,12]. Acidemia results in increased activation of the complement system, release of inflammatory cytokines (i.e., IL-1β, IL-6, or tumor necrosis factor-α) produced by mononuclear cells, and neutrophil activation and hydrogen peroxide production. The effect of acidemia on inflammation is mediated in part by proton-sensing G protein−coupled receptors, including OGR-1, G-protein receptor 4 (GPR4), and T cell death−associated gene 8 (TDAG8) [60]. In mice, GPR4, expressed in endothelial cells, has minimal activity at pH >7.4, but its activity increases at pH 7.4 and progressively rises more as the pH falls [61]. This leads to the release of multiple inflammatory chemokines and cytokines. Reducing the GPR4 genetically or with small molecule inhibitors blunts this response. Genetic knockout of TDAG8 in mice led to diminished IL-1β production from glial cells in response to acidosis [24]. As with the albumin response, the effect of acidemia to increase inflammation appears to be modifiable by more powerful systemic signals. However, acute local declines in interstitial pH have been linked to critical events in chronic disease such as rupture of atherosclerotic plaques and neutrophil activation in acute asthma [10]. Whether chronic systemic acidemia can provoke these same events to drive disease progression has not been adequately studied.

Endocrine responses to acidemia

Much attention has been given to acid-induced changes in the function of endocrine organs, including the release of cortisol, insulin, thyroxin, IGF-I, aldosterone, and PTH [62]. In many cases, activation of endocrine responses enhances the ability of bone to buffer acid and the normal kidney to excrete acid, but the same responses can cause catabolism and contribute to uremic symptoms [28,63]. In advanced kidney disease, other uremic toxins can interact with endocrine mediators, and acidemia often has an additive effect on these endocrine responses.

Acidemia increases circulating adrenal cortical hormone levels [28]. Adrenocorticotropin (ACTH) levels rise after an infusion of inorganic acids and stimulate the production of both glucocorticoids and aldosterone [64]; serum ACTH increases in acute respiratory acidosis [65]. There may also be a direct effect of low pH on the adrenal gland to stimulate the release of aldosterone, a response that depends on an increase in intracellular calcium [66]. Since both cortisol and aldosterone increase renal acid excretion in subjects with normal renal function [67,68], the rise in ACTH can be seen as a homeostatic mechanism that acts to raise net acid excretion (NAE). Acidemia also appears to lower 11β-hydroxysteroid dehydrogenase activity in aldosterone-sensitive cells in the kidney. This prevents the destruction of cortisol and enhances its capacity to activate the aldosterone receptor [69]. Interestingly, acidemia is not the only cause of elevated glucocorticoid levels in uremia, since adding bicarbonate to the diet to block the development of acidosis in rats with CKD does not normalize glucocorticoid production [36]. This uremia-associated stimulation of glucocorticoid production is a crucial factor that induces abnormalities of calcium and protein metabolism [70].

Aldosterone may also play a role in the complications of uremia. With a reduction in glomerular filtration rate, increases in plasma levels of both endothelin and aldosterone have been reported in human subjects, and this increase is ameliorated with the addition of alkali [71]. Reports indicating that spironolactone can help prevent mortality in patients with congestive heart failure suggest that aldosterone might contribute to some of the cardiovascular complications seen in kidney failure [72]. Animal studies also suggest that aldosterone may be involved in progression of renal disease [73]; how endothelin may be involved in this response in humans is reviewed in Chapter 19, Alkalization to Retard Progression of Chronic Kidney Disease. Although metabolic acidosis stimulates the production of catecholamines, glucocorticoids, aldosterone, and endothelin, supplementation of the diet of mildly hypertensive patients without kidney disease with potassium chloride is equally as effective as potassium bicarbonate at lowering blood pressure [74]. As discussed later, a net acid diet may not be a sufficiently potent stimulant of these mediators to induce clinically measurable hypertension in humans with normal renal function.

Metabolic acidosis suppresses the cellular signaling and clinical effects stimulated by both insulin and IGF-I in different ways. Acidemia does not alter islet cell secretion of insulin but does induce resistance to insulin action in peripheral tissues; reversal of metabolic acidosis improves the sensitivity of glucose metabolism to insulin [75]. In contrast, metabolic acidosis reduces growth hormone release from the pituitary and this leads to lower levels of IGF-I production. The response to an infusion of physiological concentrations of growth hormone is very mildly impaired in metabolic acidemia, and larger concentrations of growth hormone completely reverse the effects of metabolic acidemia. Two factors appear to blunt the response to administered growth hormone: first, the density of

IGF-I receptors in muscle is lowered by acidemia and, second, there is a defect in the signaling that results from the binding of IGF-I [76–78]. IGF-I resistance in uremia does not improve with the correction of metabolic acidosis suggesting that separate mechanisms (possibly involving corticosteroids) play a role [48,79]. Administration of superphysiological doses of growth hormone reduces renal nitrogen loss [80]. IGF-I (like insulin) is a major determinant of amino acid release from the muscle, although part of the beneficial response on nitrogen balance may involve improvement in plasma cortisol and/or aldosterone levels [81]. These studies point out how complex interactions occurring between different endocrine mediators can work together to either exacerbate or relieve the effects of acidemia. Abnormalities in insulin and IGF-I actions also play an important role in the growth suppression seen in children with metabolic acidosis [82].

Metabolic acidosis also suppresses adiponectin levels in subjects ingesting oral ammonium chloride. This is important because adiponectin increases insulin sensitivity and enhances its antiatherogenic and antiinflammatory properties [83]. Beyond its effect on adiponectin, metabolic acidosis decreases secretion of leptin by adipocytes [84]. Taken together, these changes induced by metabolic acidosis should promote protein catabolism, decrease protein synthesis, and promote negative nitrogen balance. In the 1999–2000 and 2001–02 National Health and Nutrition Examination Surveys, insulin sensitivity was estimated by an index based on fasting insulin and triglyceride levels [85]. Lower serum bicarbonate levels and a higher anion gap were found to be independently associated with insulin resistance. However, insulin sensitivity was not measurably improved by bicarbonate supplementation in healthy older subjects despite the improvement in their muscle strength [86,87]. Again, it is possible that a net acid diet is insufficient to induce clinically measurable insulin resistance; frank acidemia may be necessary. Further studies will be needed to define the clinical importance of net acid diets versus frank acidemia on insulin resistance and its synergy with such other factors as obesity, glucocorticoids, and uremia.

Both metabolic and respiratory acidosis increase the sensitivity of the parathyroid gland to changes in ionized calcium and also stimulate release of PTH [88,89]. PTH has long been known to increase renal net acid secretion by inhibiting renal tubular bicarbonate resorption [90]. In patients with normal renal function, metabolic acidosis decreases proximal tubular phosphate reabsorption resulting in hypophosphatemia, and this may cause a secondary stimulation of 1,25-dihydroxyvitamin D production. The resulting rise in the activity of vitamin D counteracts the direct effects of metabolic acidosis to increase PTH secretion, so that serum PTH concentrations are usually unchanged or even fall slightly with metabolic acidosis [91]. In ESRD, metabolic acidosis has almost no effect on phosphate excretion or 1,25-dihydroxyvitamin D production because of the loss of kidney function. Instead, metabolic acidosis increases PTH by a direct stimulatory effect on the parathyroid glands [25,88]. Importantly, correction of metabolic acidosis in patients on hemodialysis who have secondary hyperparathyroidism increases the ability of calcium to suppress the parathyroid gland's release of PTH [88]. In patients with moderate CKD, correction of metabolic acidosis with sodium bicarbonate has been shown to attenuate the rise in PTH and serum urea nitrogen levels [92].

Similar to uremia, metabolic acidosis lowers serum levels of the thyroid hormones, free T3 and T4, but, unlike uremia, may slightly raise reverse T3 (59,60) [93,94]. Resistance to the effects of thyroid-stimulating hormone (TSH) occurs within the thyroid gland and is associated with elevated levels of TSH and thyroid-releasing hormone. That these alterations in thyroid function are sensitive to metabolic acidosis is underscored by their correction with alkali [95]. While the clinical significance of this acidemia-induced mild hypothyroid-like response is unknown, it has been speculated that it plays a counter regulatory role reducing muscle proteolysis [96]. However, hypothyroidism also reduces muscle protein synthesis to leave overall muscle metabolism unchanged [97]. Furthermore, there is some evidence that hypothyroidism increases cardiovascular risk in uremia [98]. There is also little or no effect on bone. Thus while this response appears to be an exception to the overall paradigm of hormonal alterations contributing to acid-induced catabolism, the effect of acidosis on thyroid hormone may not be benign.

Renal hypertrophy

Although metabolic acidosis increases the activity of the ubiquitin–proteasome system in muscle leading to wasting, the response to metabolic acidosis in the kidney is associated with decreased lysosomal proteolysis and renal growth. Metabolic acidosis suppresses protein breakdown in both intact renal cortex and in suspensions of isolated proximal tubules [99]. The high ammonia concentrations present in metabolic acidosis suppress lysosomal proteolysis in cultured renal tubular cells and cause increased accumulation of proteins that are normally destroyed in lysosomes [100,101]. Shechter and coworkers examined rats fed with ammonium chloride and found that there is a decrease in lysosomal cathepsin activity in the renal cortex [99].

Thus many of the amino acids that are lost from muscle during metabolic acidosis are metabolized to ammonia in the kidney, and this latter process stimulates kidney growth [103]. Much of these amino acids are first converted to glutamine in the liver that directly provides the ammonia to the kidney. Hypertrophy of the kidney is also driven by endocrine changes that occur in acidemia, including the activation of the renin−angiotensin−aldosterone system, cortisol, and endothelin [104]. All of these changes, along with the activation of complement and inflammatory pathways, may contribute to progressive kidney damage and loss of kidney function.

What is the benefit of the catabolic response to metabolic acidosis?

Given the strength and sensitivity of the catabolic response to acidemia or an acid load, it is worth asking the teleological question: what outcomes could have driven the evolution of such a response? As reviewed earlier, the catabolic response to chronic acidemia helps drive the buffering and excretion of excess hydrogen ions [27]. This response is consistent with a net acid diet producing many of the same effects as frank acidemia. The calcium carbonate apatite of bone directly dissolves with acid and the hormonal responses accelerate this buffering process. The liberation of amino acids from muscle allows for increased liver glutamine production and net renal acid secretion in the form of ammonium.

A second benefit of the response to acidemia comes from the role of acidosis caused by ketone formation in the catabolic response to starvation [105,106] (Fig. 10.2). As glycogen stores are depleted during starvation, the decrease in insulin levels triggers a transition in metabolism to ketone body formation [106,107]. The acid formed from the ketone bodies leads to changes in intracellular energy, redox sensing systems, and intracellular insulin signaling that contribute to a reduction in the basal metabolic rate [106]. Phosphate from bone and amino acids from solid organs and muscle maintain serum phosphate and amino acid levels. In the absence of ketosis, amino acids are used sparingly for energy; additionally, visceral organs, not muscle, provide the bulk of the amino acids. Oxidizing amino acids for energy is energetically unfavorable due to the high metabolic cost of urea formation [108]. In contrast, acidity from ketosis stimulates glucose formation from renal deamination of glutamine. Glucose from glutamine is energetically favorable, because nitrogen is directly excreted in the form of ammonium without further metabolism to urea [109]. Production of urea from glutamine may use 30% of the ATP generated from its metabolism, whereas ammoniagenesis may use only about 7%. Thus the integrated catabolic response to acidemia allows energy conservation in the production of glucose from BCAA in starvation.

A third potential benefit is in the proinflammatory role of acidemia in resisting infection and promoting tissue regeneration [12]. Why would acid provoke an antiinfectious response? Metabolic acidosis, whether from diarrhea, ketosis, or lactic acidosis, is among the most common laboratory abnormalities in critical illness [11]. Tissue ischemia with local acidemia occurs during systemic and local infection, trauma, and in cardiac and cerebrovascular diseases—all conditions where local inflammation acts as part of the response to injury or infection and contributes to the recovery process [10]. Acidemia liberates amino acids from

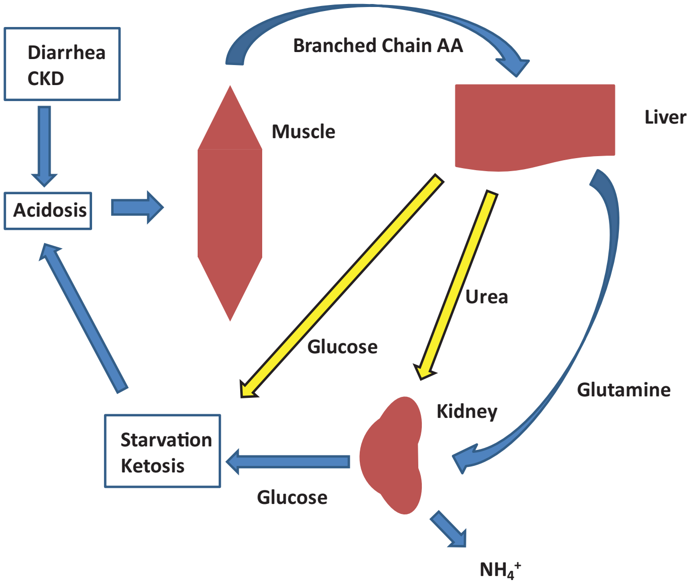

FIGURE 10.2 Starvation and acidosis alter gluconeogenesis from amino acids. In the fed state, excess amino acids are converted to glucose via the urea cycle (yellow). Urea formation has an energetic cost of ~35% of the energy of the glucose formed. In starvation (blue), ketone formation leads to a mild acidosis enhancing the release of branched-chain amino acids from muscle. During acidosis the liver preferentially converts branched-chain amino acids to glutamine, which is deaminated in the kidney to produce ammonium and glucose. Glucose production from glutamine is much more energetically favorable than the urea cycle making this response adaptive in starvation. Metabolic acidosis from other causes activates the same pathway leading to the excretion of hydrogen ions via ammonium at the cost of amino acids. *CKD*, Chronic kidney disease.

muscle to enhance immune responses when fighting infection [4]. Although acidemia is beneficial in acute illness, it becomes a liability in driving inflammation in CKD [110].

Theories of subclinical acidemia, acid stress, or eubicarbonatemic metabolic acidosis

Even small degrees of acidemia drive catabolism: bone mineral and muscle protein are used to buffer and aid excretion of excess acid to maintain normal intercellular and extracellular pH [111]. These responses to an acid load can also occur even when blood bicarbonate levels are within normal range: a fact that led to theories that consuming a net acid diet may have similar, but milder, effects as acidemia itself. Consuming acid loads may not rapidly lead to the full endocrine disruption of frank acidemia, but a net acid diet may play a role in the development of milder complications over a longer period of time [112]. Even in subjects without overt CKD, supplementing their net acid diet with alkali is anabolic for both muscle and bone [113,114]. These findings have led to the theories of subclinical, acid stress, or eubicarbonatemic, metabolic acidemia.

The concept of subclinical metabolic acidemia explains the beneficial effects of giving alkali to both CKD subjects and the general population who have normal serum bicarbonate levels. Administration of base can induce anabolic effects in the subset of these individuals who have an arterial blood pH below 7.40 [115]. Most studies only measure bicarbonate or total CO_2 where the normal range of values is often listed as extending 2 mEq/L below the mean "normal value" of 24 mEq/L [116]. Thus some individuals who have a serum bicarbonate apparently in the normal range have bicarbonates concentrations less than 24 mEq/L and thus may have pH under 7.40. The measurement of mild or subclinical acidemia may be best performed with arterial or venous blood gasses to be certain that an arterial blood PCO_2 less than 40 mmHg is not present. Careful studies in animal models strongly support this hypothesis: there appears to be an anabolic benefit of giving base in only mildly acidemic rats [27]. Small-scale human studies on nitrogen balance also support this concept. For example, a randomized, crossover study in eight peritoneal dialysis patients showed that a targeting arterial pH to 7.43–7.45, as compared to pH of 7.36–7.38, is associated with more positive nitrogen balance [117]. Human outcome studies adequately powered to address this issue have used mortality and CKD progression endpoints rather than bone or muscle parameters. Human epidemiologic studies measuring serum bicarbonate do not show an effect of bicarbonate levels of 22–23 mEq/L on mortality whereas studies using arterial blood gas show a 24% higher all-cause mortality, with a bicarbonate under 25 mEq/L [118,119]. No definitive clinical trials have been designed to address this issue, but the Use of Bicarbonate in Chronic Renal Insufficiency trial is at least consistent with this hypothesis [120]. In subjects with CKD stages 3–5, correction of bicarbonate to 24–28 mEq/L from a baseline mean of 21.9 mEq/L (range 18–24) resulted in a mortality benefit.

Theories of acid stress or eubicarbonatemic metabolic acidosis extend the benefit of base to individuals with normal serum acid/base status, but who are retaining acid in their tissues [27,121]. Careful pH measurements of interstitial muscle fluid reproducibly identify individuals with serum pH >7.40 but interstitial pH <7.40 [121]. These individuals show alterations in urine NAE consistent with acidemia; they show some evidence of increased anabolism when they are supplemented with base or when their net dietary acid load is decreased. In the AASK trial, subjects with a serum bicarbonate of >22 mEq/L had a higher mortality when they had lower, not higher, net acid secretion, suggesting that the inability to rapidly excrete an acid load is associated with increased mortality [122]. Decreased urinary ammonium and urinary citrate levels appear to be key markers of individuals at a higher risk of dying. Individuals with hidden acidemia have lower urinary citrate excretion that increases with base supplementation [123]. These theories predict that renal disease, by reducing capacity for excretion of acid, prolongs the catabolic effects of dietary acid. This hypothesis could explain the increase in catabolism as CKD worsens. While there are few direct studies addressing this, analyses of the published studies suggest that the beneficial effects of correction of acidemia or lowering dietary net acid load are greater in CKD 4–5 than in CKD 1–2.

Estimated net endogenous acid production and the potential renal acid load

Measurements of the effects of dietary net acid load are largely based on estimating the amount of acid the kidney must excrete to maintain homeostasis: about 40–120 mEq/day on a Western diet [124,125]. While positively charged amino acids are metabolized to acid and negatively charged ones are metabolized to base, the sulfur-containing amino acids, methionine and cysteine, produce the majority of metabolic acid. Thus the sulfur-containing amino acid content of the food is an excellent surrogate for dietary acid load, except when acid phosphates are used as food additives. The base in the diet comes largely from fruits and vegetables that contain organic acids (citrate, acetate, malate, etc.) that liberate CO_2 after metabolism in the Krebs cycle [126]. However, plant fiber increases stool loss of bicarbonate and other organic bases that also contribute to the acid load. When all factors are considered, fruits and vegetables contain a large amount of net alkali; milk can be mildly acidic to alkaline depending on the species; and meat, fish, and grain have a net acid value (Table 10.2) [127]. Note that if a subject is in positive nitrogen balance (e.g., during growth in childhood, pregnancy, or exercise), some amino acids are not metabolized, lowering the net acid load of the diet.

The renal net acid load can be directly measured by 24-hour urine pH, titratable acidity, ammonium, and organic acids [125,126]. However, ammonium and organic acids can be difficult to measure, so several methods have been used to estimate dietary net acid load. Estimated *net endogenous acid production* (NEAP) is the simplest and most widely used in epidemiologic studies [128]. It uses dietary protein to estimate the sulfuric acid content of the diet and potassium to represent the fruit and vegetable content:

$$\text{Estimated NEAP}(\text{mEq/day}) = -10.2 + 54.5(\text{dietary protein}(g/\text{day})/\text{potassium}(\text{mEq/day}))$$

The usefulness of this equation arises from the large number of available epidemiologic and clinical trial databases that include dietary protein and potassium. It was derived and verified in populations consuming a Western diet and may not be accurate for other diets. It is confounded by an absolute dependence on components that have independent effects on health outcomes: protein and potassium intake.

Because accepting a hydrogen ion (i.e., by a base) leaves a cation, while releasing a hydrogen ion (i.e., by an acid) leaves an anion, differences in ions that are completely dissociated at physiologic pH (called strong ions) can be used to more accurately estimate dietary net acid load [125]. The ion composition of food can be estimated from dietary intake measures found in clinical trial databases (e.g., 24-hour recall, food frequency questionnaires) to calculate an acid load [129–131]. As dietary recall methods sometimes have quantitative errors [132], many investigators use 24-hour urine ion measurements for this estimate. The best validated equation is the *potential renal acid load* (PRAL) [129]. It estimates the sulfur content from total dietary protein with a correction for dietary phosphorous. The potential base load calculated from the strong ions is subtracted from the acid load.

$$\text{PRAL}(\text{mEq/day}) = 0.49 \times \text{protein}(g/\text{day}) + 0.037 \times \text{phosphorous}(\text{mg/day}) - 0.21 \times \text{potassium}(\text{mg/day}) - 0.026 \times \text{magnesium}(\text{mg/day}) - 0.13 \times \text{calcium}(\text{mg/day})$$

The PRAL, used with 24-hour urine values, also correlates with measured renal net acid load, but the correlation is not linear. Urinary excretion of organic acids (e.g., citrate) leads to loss of base, so an adjustment to PRAL based on the loss of organic acids has been proposed [133]. This correction may also account for stool losses. The correction factor (OA) for these organic acids on acid/base balance was empirically measured from NAE, OA = body surface area × 41/1.73 [133]. This formula correlates with estimated intake from food frequency questionnaires and with 24-hour urine measurements.

TABLE 10.2 Estimated potential renal acid load (PRAL) of common foods (related to 100-g edible portion).

Food	PRAL		PRAL
High alkali-containing foods		**High acid-containing meals**	
Raisins	−21.0	Cheddar, cheese	26.4
Black currants	−6.5	Cheese, gouda	18.6
Orange juice	−2.9	Egg, yolk	23.4
Celery	−5.2	Parmesan	34.2
Radish	−14.0	Chicken, meat only	8.7
Carrots, young	−4.9	Bean, lean only	7.8
Cauliflower	−4.0	Chocolates, milk	2.4
Spinach	−14.0	Rice, brown	12.5
Zucchini	−4.6	Trout, brown, steamed	10.8
Red wine	−2.4	Bread, white wheat	3.7

Source*: Reproduced from Remer T, Manz F. Potential renal acid load of foods and its influence on urine pH. J Am Diet Assoc 1995;95:793.*

Thus the best current estimate of renal net acid load using the 24-hour urine ion excretion is as follows:

$$\text{Estimated renal net acid load} = \text{PRAL} + \text{OA}$$

PRAL-based equations are significantly more accurate measures of net acid load than estimated NAE and are extremely useful for calculating the net acid content of individual foods. However, the equation's accuracy is also its weakness in epidemiologic studies. Because protein, fruits, and vegetables are the actual source of the acid and base in the diet, epidemiologic results using PRAL-based equations are confounded by nonacid/base effects of protein, fruit, and vegetables. As with lower protein diets, lower PRAL diets in patients with CKD were associated with a significantly reduced risk of progression to ESRD [134]. Similar to increased vegetable intake, lower PRAL diets in the general population are associated with a lower incidence of hypertension [135] and peripheral vascular disease [136], with increased physical activity and decreased frailty [137], and decreased incidence of diabetes [138]. Other endpoints have more mixed results, possibly reflecting differing effects of protein, and fruits and vegetables. In the general population, PRAL had a U-shaped association with both cardiovascular and all-cause mortality [139]. The higher mortality in low PRAL diets could reflect inadequate protein intake and the higher mortality in high PRAL diets inadequate vegetable intake. Higher PRAL in the Framingham cohort is only associated with decreased bone mineral density in older men, but not younger men or women [140]. In this same cohort, higher dietary protein intakes were associated with improved bone mineral in women but worsening bone density in older men [141], whereas vegetables are beneficial in both groups [142]. Thus the beneficial effect of higher protein intakes on bone density in older women may be masking a deleterious effect of dietary acid load on bone density [143].

Thus these studies support the benefits of a dietary pattern of adequate, but not excessive protein, in the setting of adequate intake of fruits and vegetables [144]. Lower net acid load, by preventing catabolism and limiting inflammation, may only be one of many benefits of this dietary pattern. It is frustrating, from an academic standpoint, that we cannot prove that the lower acid load leads to specific benefits, but clinically it may not matter. This pattern, which forms the basis of Dietary Approach to Systolic Hypertension and Mediterranean diets [145], gives us a powerful tool for disease prevention (see Chapter 37: Nutrition and Blood Pressure).

Clinical implications for calcium and bone

Chronic metabolic acidosis causes increased proximal tubule citrate reabsorption leading to hypocitraturia [146]. The combination of increased renal calcium losses and hypocitraturia results in an increased incidence of nephrolithiasis [27,147,148]. In addition to the higher incidence of nephrolithiasis, preoperative metabolic acidosis has been associated with a higher incidence of osteoporosis and fractures in patients undergoing radical or partial nephrectomy [149]. Alkalemia, while associated with lower urine calcium, can raise urine pH to over 6.9 where calcium phosphate becomes less soluble leading to calcium phosphate nephrolithiasis or tubular deposition of calcium [150].

Although there are no randomized controlled trials evaluating the effect of metabolic acidosis and CKD on the growth of children, multiple observational studies and clinical experience strongly suggest that the catabolic effect of acidemia on bone is of great clinical importance in suppressing bone growth [151]. The best evidence is catch-up growth observed when acidosis is corrected in acidotic children with impaired growth. Sustained correction of acidosis results in restoration of height to normal in pediatric patients with classic renal tubular acidosis and growth impairment [152]. Consequently, correction of acidosis is recommended before initiation of growth factor therapy. Acidemia may have a particular effect on the chondrocytes in the growth plate [153]. In rats, 14 days of metabolic acidosis reduced new bone formation that was associated with a specific defect in the height of the hypertrophic zone of the growth plate. Acidosis reduced both cartilage production and bone formation.

In patients with CKD or ESRD the excess calcium mobilized from bone in the setting of acidosis remains in the extracellular space and raises the theoretical possibility of ectopic calcification. However, it has long been known that metabolic alkalosis rather than acidosis predisposes to uremic ectopic calcification [154]. In uremic rats given vitamin D, metabolic acidosis inhibits soft-tissue calcification. In the absence of metabolic acidosis, vitamin D administration to rats with a similar degree of uremia results in significant calcification in the aorta, stomach, and kidney, and higher mortality results [155]. Studies in cultured rat aortas suggest that the decrease in calcium phosphate solubility with alkaline pH, and not secondary hormonal changes, augments vascular calcification [156]. In vivo, the decrease in ionized calcium with alkalemia partly counters the lower solubility of calcium phosphate as pH rises. In normal individuals, metabolic alkalosis is not associated with ectopic calcification, despite a decrease in urinary calcium excretion [157]. The calcium–alkali syndrome (formerly called the milk–alkali syndrome) results when alkalemia is combined with excessive calcium intake [158,159]. Despite the reduction in urinary fractional excretion of calcium and the stimulation of citrate excretion, the rise in filtered load of calcium and high urinary pH can lead to nephrocalcinosis and nephrolithiasis. In both CKD and hypercalcemic individuals with normal renal function, alkalemia appears to be a greater risk than acidemia for ectopic calcification.

In summary, correction of acidosis with alkali has been shown to improve bone mineralization and histology in acidotic patients, including those treated by hemodialysis [160]. The response of other organ systems to metabolic acidosis can lead to deleterious effects on bone mass. For example, metabolic acidosis–induced muscle catabolism can lead to decreased muscle mass that decreases the physical load on bone, leading to decreased stimulation for bone growth. Further, decreased 1,25-dihydroxyvitamin D levels, decreased growth hormone sensitivity, and increased glucocorticoid activities in response to metabolic acidosis can lead to decreased bone mass [23]. Still, it has not been documented that reduced fracture rates or other outcomes are correlated with improved acid–base status in dialysis patients. The two major concerns with alkali therapy are ectopic calcification, especially in patients with CKD or hypercalcemia, and arrhythmias in patients with hypokalemia or hypocalcemia. The observation that patients with overt alkalosis have higher mortality than those with normal serum bicarbonate suggests caution in overcorrection of acidosis with alkali [119]. Further studies will be needed to determine how to obtain the benefits of alkali therapy on bone while minimizing risks of ectopic calcification.

Clinical implications for protein nutrition, muscle function, and mortality

How does metabolic acidosis affect nutritional status? It has long been felt that anorexia contributes to protein wasting in patients with metabolic acidosis, but it has been difficult to quantify the relative contribution of anorexia to protein malnutrition in acidemic people. On the other hand, strong evidence exists that excessive muscle protein catabolism due to a large increase protein degradation coupled with a smaller decrease in protein synthesis is the dominant mechanism for loss of lean body mass in metabolic acidemia. First, in rats with chronic renal failure, high-protein diets were associated with metabolic acidosis, stunted growth, and a lower efficiency of using dietary protein for growth [103]. Second, in poorly growing infants with metabolic acidosis, nitrogen excretion does not correlate with protein intake suggesting that their poor nitrogen balance is due to increased catabolism rather than decreased diet [161]. Third, normal adults with experimentally induced metabolic acidosis who are eating a constant diet exhibit both increased oxidation of the essential BCAA and protein degradation [31]. Fourth, chronic hemodialysis and CAPD patients with acidosis exhibit excessive protein catabolism that can be suppressed when acidosis is corrected with dietary alkali supplements [162,163]. Fifth, in chronic hemodialysis patients, there is a strong linear correlation between the degree of acidosis measured just before a dialysis treatment and the free valine concentration in a muscle biopsy [164]. Treating dialysis patients with sodium bicarbonate raises the levels of BCAA in muscle; this strategy may provide more essential amino acids that can be used in the synthesis of muscle protein [165]. Besides taking supplements of sodium bicarbonate, dialysis patients experience a reduction in the severity of metabolic acidosis when they are fed a low net acid load diet. Either strategy is effective, because both improve nitrogen balance and raise the plasma concentrations of the BCCA [166,167].

There is growing evidence that exercise may ameliorate or reverse some muscle disorders related to CKD. In rat studies, muscle mass can be increased through the use of isometric exercise [168]. Exercise induces insulin-independent amino acid entry into muscle cells, reducing the catabolic effect of acid on muscle [169], and leads to the release of myokines that reduce the inflammatory effects of acidemia [170]. This combination of effects explains why a high dietary protein intake, which raises dietary PRAL, leads to anabolism when combined with resistance exercise [171]. However, acidemia may limit some of the beneficial effects of exercise on muscle. In the setting of metabolic acidosis, exercise may transiently worsen the metabolic acidosis and may decrease the normal anabolic effects of exercise [172]. Patients with CKD stages 3 and 4 with serum bicarbonate levels of 20–22 mEq/L had a greater rise in blood pressure and faster time to fatigue during rhythmic handgrip exercise when compared to those with a serum bicarbonate of >24; there was no difference in intramuscular pH between the two groups [173]. It is not clear whether these observations carry over to the general population. In competitive sports, alkali is now widely seen as a performance enhancing drug for competition [174]. However, the doses used (0.3 g of sodium bicarbonate/kg body weight) push competitors into frank alkalemia, raising the possibility of a pharmacologic effect. While base is widely used in training diets to attenuate the acid load of high-protein diets, and hormonal changes have been described, the effect on muscle anabolism of alkali administered before the exercise commences is unclear. For example, the addition of bicarbonate prior to high-intensity exercise appears to attenuate both the exercise-induced anabolic human growth hormone and catabolic cortisol responses [175].

In addition to improved muscle function, correcting acidemia may have benefits on cardiovascular fitness. In the general population, persons chronically consuming a lower PRAL diet had a higher respiratory exchange ratio during maximal effort exercise, suggesting a greater maximal oxygen uptake [176]. These findings may have relevance for CKD patients undergoing rehabilitation therapy. The association of acidosis with functional outcomes was examined in the National Health and Nutrition Examination Surveys 1999–2002. Serum bicarbonate and gait speed determined from a 20-ft timed walk were measured in over 2500 adults, age 50 years or older. Lower serum bicarbonate levels were associated with slower gait speed and decreased quadriceps strength in older adults (109) [177]. In the prospective Health, Aging, and Body Composition study, a serum bicarbonate less than 26 mEq/L was associated with increased risk of functional limitations defined as difficulty in walking 0.25 mi or climbing 10 steps [178].

In epidemiologic studies the U-shaped association between mortality and serum bicarbonate shows higher mortality with metabolic acidosis, respiratory acidosis, and metabolic alkalosis [119]. The increase in mortality with metabolic alkalosis may reflect the underlying morbid conditions that maintain a metabolic alkalosis (e.g., heart failure, volume depletion, and hyperaldosteronism) or may be the contribution of alkalemia to vascular calcification. Acidemia could similarly be an indicator of a high mortality condition, such as CKD or intestinal malabsorption. But since acidemia induces muscle wasting, decreased muscle function, and inflammation, it also drives protein-energy wasting that is associated with increased mortality [4]. However, again, it is not certain whether protein-energy wasting causes increased mortality or simply indicates underlying morbid conditions that engender the mortality.

Clearly, muscle protein reserves are critical for surviving acute infectious illnesses; functional status predicts mortality in chronic dialysis patients, and CRP is a marker for increased cardiovascular risk in these individuals. A recent clinical trial suggests that acidemia causes increased mortality in CKD patients. The Use of Bicarbonate in Chronic Renal Insufficiency was a multicenter, randomized, unblinded, pragmatic, and controlled trial that enrolled in each treatment arm approximately 370 patients with CKD stages 3–5 and with serum bicarbonate levels between 17 and 24 mEq/L [120]. The interventional arm received sufficient sodium bicarbonate to maintain the serum bicarbonate level at 24–28 mEq/L as compared to the usual treatment arm that had mean serum bicarbonate levels of about 22 mEq/L throughout the study. At 36 months of follow-up, there were significantly fewer deaths in the interventional arm (12% or 3.1%) as compared to the usual treatment arm (25% or 6.8%). Respiratory acidosis also carries a high mortality, but it is unclear, if this reflects lung or neurologic disease versus the effects of acidosis on muscle or other tissues. For example, acidemia was associated with decreased survival in a cohort of patients with chronic obstructive pulmonary disease, but acidemia was no longer an independent risk of death when hypoxia was considered [179].

Treating metabolic acidosis

Metabolic acidosis of CKD can be treated by decreasing intake of dietary acid-producing animal-based proteins, increasing intake of alkali-producing fruits and vegetables, and/or adding alkali salts [180] (see also Chapter 19: Alkalization to Retard Progression of Chronic Kidney Disease). Limiting protein intake is effective at correcting acidemia. Considerations on the use of low protein diets in CKD are discussed in Chapters 16, 29, and 30. Dietary patterns with increased dietary vegetable intake correlate consistently with an up to 25% decline in all-cause mortality, improvements in cardiovascular endpoints, reductions in blood pressure (see Chapter 37: Nutrition and Blood Pressure), and improvements in bone health [181]. Higher fruit intake has much smaller benefits in these same areas. Increasing dietary alkali (fruits and vegetables) increased serum bicarbonate levels in patients with stages 1–3 CKD [182,183] and patients with hypertensive CKD [184] with the added benefit of decreasing blood pressure [183]. Thus for both the general population and patients with CKD stages 1–4, increasing dietary vegetable intake, with increases in fruit as tolerated, should be the first intervention and done even in patients with normal serum bicarbonate. Given the potential for hyperkalemia in patients with advanced CKD, careful monitoring of potassium is required when increasing dietary fruits and vegetables in these patients. As plant-based diets also have advantages for controlling dietary protein intake in advanced CKD, more centers are using drugs to enhance potassium excretion with high vegetable diets [185] (see also Chapter 21: Management of Potassium in Chronic Kidney Disease and Acute Kidney Injury). With fruits and starchy vegetables, diabetic patients may need supervision of portion size and timing of insulin dosing.

There is currently no clinical consensus on the optimal correction of acidemia. The abovementioned data suggest that treating acidemia to a target of pH of 7.40 (bicarbonate >24 mEq/L) is necessary and sufficient to control catabolism. But when is diet not enough, and when should we start supplemental base? Many experts recommend that nondialyzed CKD patients and MHD and chronic peritoneal dialysis patients should start sodium bicarbonate supplements when serum bicarbonate levels are <22 mEq/L, with a goal to attain a normal bicarbonate level ≥ 24 mEq/L [180]. This is consistent with the design of the Use of Bicarbonate in Chronic Renal Insufficiency trial [120]. However, some clinical trials have used the bottom of the normal range (serum bicarbonate = 22 mEq/L) as a treatment goal, suggesting that such conservative treatment may avoid side effects [186].

Based on these and other studies, the KDOQI Clinical Practice Guidelines for Nutrition in Chronic Kidney Disease suggest a dietary pattern of high intake of fruits and vegetables for patients with CKD 1–4 [187]. This suggestion, at level 2C, reflects the relatively low quality of the evidence on long-term outcomes in the CKD population. The KDIGO evidence rules did not allow consideration of the enormous benefit of this dietary pattern in the general population, which includes large numbers of people with CKD stages 1–3. Thus our recommendation for this dietary pattern is stronger than theirs. Further, in adults with CKD 3–5D, the KDOQI Clinical Practice Guideline recommend at the level 1C reducing net acid production through increased bicarbonate (alkali) supplementation [187]. This stronger recommendation is based on the larger benefit seen with correction of acidosis in patients with more advanced kidney disease and the extensive safety data with bicarbonate usage. We are in agreement with this recommendation.

This leaves the question of how to use alkali therapy for patients with subclinical metabolic acidosis. This may be resolved with further study. Some researchers have argued that targeting serum bicarbonate closer to the upper limit of the reference range (26–30 mEq/L) may have even greater benefit for patients with protein-energy wasting and eubicarbonatemic metabolic acidosis [188]. The major concern about such recommendations is the lack of information regarding the long-term effects of chronic metabolic alkalosis [189] and the association, whether causal or not, of alkalemia with increased in mortality in the CKD population [119]. The recent KDOQI guidelines suggest a bicarbonate goal of 24–26 mEq/L, but with the level of confidence given only as *opinion* because of the lack of adequate clinical trials [187]. However, several of the trials cited in this chapter were published after the closing date for the KDOQI evidence search, and the results of at least one of these trials suggest that a serum bicarbonate concentration of 25–27 mEq/L may be the preferred goal. As discussed earlier, there is also no consensus on how to model bicarbonate delivery with hemodialysis to adequately treat acidemia, but that acute alkalemia postdialysis should be avoided [20].

Sodium bicarbonate is the most commonly used alkali salt for treating metabolic acidosis [180]. Following oral ingestion, sodium bicarbonate neutralizes gastric acid (HCl) to form sodium chloride (NaCl), CO_2, and water. Excess bicarbonate, not neutralized by gastric acid, is absorbed from the small intestine into the systemic circulation. Oral sodium bicarbonate is relatively inexpensive and well tolerated. Side effects of sodium bicarbonate reported in CKD patients include bloating, flatulence, and belching, which can be attributed to the release of CO_2. Sodium bicarbonate may lower serum potassium making it ideal for adding to a high fruit and vegetable diet. Unlike high plant diets that provide an alkaline load, which is associated with a tendency to decrease blood pressure, oral sodium bicarbonate to correct acidemia did not lower blood pressures in clinical trials. Moreover, increased blood pressure and edema due to $Na+$ ingestion were not seen in these trials [56,120,182,184]. This observation is consistent with older studies showing more effective excretion of sodium when given as sodium bicarbonate than sodium chloride [190]. Lower mortality within the sodium bicarbonate treatment arm in some studies suggests greater safety [120]. However, uncontrolled blood pressure and heart failure have been exclusion criteria for these studies, so sodium bicarbonate therapy should be monitored closely in these populations. Sodium citrate, an alternative alkali salt, may have more limited use due to its potential for enhancing intestinal aluminum absorption and its taste, which is unpleasant for some people [191]. Finally, Na retention still is a concern with sodium base treatment in patients with ESRD.

Potassium bicarbonate and potassium citrate are both well tolerated in patients who are in the early stages of kidney disease, who have hypokalemia secondary to diuretics, or who have chronic gastrointestinal bicarbonate loss [192]. The availability of potassium base as citrate or bicarbonate in wax matrix, dissolvable, and liquid formulations increases the likelihood of finding a tolerable treatment However, high alkali diets are the preferred method of delivering potassium with base. A new class of hydrochloric acid–binding resins that provide no sodium load is under development. The first clinical trial of the resin veverimer in patients with stages 3 and 4 CKD who had baseline serum bicarbonate levels of about 18 mEq/L showed their serum bicarbonate increased to approximately 22 mEq/L over 12 weeks [186]. There was a significant improvement in a questionnaire-based assessment of physical function. As with bicarbonate therapy, the most common side effects were minor gastrointestinal symptoms.

In summary, there is abundant evidence from experimental animals and cultured cell studies and from normal adults and CKD patients that metabolic acidosis is a major factor causing morbidity and mortality, especially in patients with CKD. On the other hand, healthy individuals experience milder effects from acidemia or high PRAL diets. The reduced adverse effects of an acid load in the general population are likely due to a lower exposure due to more effective renal excretion of acid and to hormonal or other metabolic signals, especially those activated by exercise, that overcome the catabolic effects of acidemia. Although the clinical evaluation of serum bicarbonate values is sometimes difficult and optimal bicarbonate goals are not known, the treatment of acidemia is straightforward and often results in a gain of weight, increased muscle mass, improved functional status, and improved mortality in CKD patients [191]. In short, the simple acts of restricting dietary protein or increasing fruit and vegetable consumption (before the start of dialysis) or supplementing alkali (before or after the start of dialysis) can reduce the risk of major complications of the metabolic acidosis of CKD.

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CHAPTER

11

The gut microbiome and the kidney

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> We should think of each host and its parasites as a superorganism with the respective genomes yoked into a chimera of sorts.
>
> Nobel Laureate Joshua Lederberg [1]

Case vignette

A 65-year-old man with chronic kidney disease (CKD) stage G4A1 presented to the emergency room with chronic constipation and lethargy. Clinical exam was remarkable for distended abdomen with hypoactive bowel sounds and generalized muscle weakness. Laboratory investigation revealed sodium, 138 mEq/L; potassium, 6.2 mEq/L; chloride, 115 mEq/L; bicarbonate, 16 mEq/L; anion gap, 14; serum urea nitrogen, 67 mg/dL; creatinine, 3.8 mg/dL (corresponding to eGFR 16 mL/min/1.73 m^2 by Modification of Diet in Renal Disease (MDRD) equation); glucose, 100 mg/dL; calcium, 8.1 mg/dL; phosphate, 7.1 mg/dL; albumin, 3.6 g/L; white blood cell count, 8.1×10^9/L; and hemoglobin, 10.1 g/dL. Abdominal computerized tomography (CT) showed abundance of fecal matter in a dilated rectum and sigmoid colon. After disimpaction with enema and laxatives, the patient felt better and was discharged from the emergency room with the recommendation to take stool softeners on a regular basis.

After 2 months, he was seen in the outpatient nephrology clinic. He appeared energetic and stated that he was taking a daily prebiotic, p-inulin, and along with a laxative as needed. Repeat laboratory evaluation showed sodium, 139 mEq/L; potassium, 4.0 mEq/L; chloride, 110 mEq/L; bicarbonate, 20 mEq/L; anion gap, 11; serum urea nitrogen, 51 mg/dL; serum creatinine, 3.4 mg/dL (with eGFR 18 mL/min/1.73 m^2); glucose, 82 mg/dL; calcium, 8.3 mg/dL; phosphate, 6.2 mg/dL; and albumin, 3.8 g/L.

Introduction to the gut microbiome

Approximately 10^{14} bacteria reside in the human gut, providing enormous metabolic potential [2–4]. The term “microbiota” refers to the group of bacteria, bacteriophages, fungi, protozoa, and viruses that live in or on the human body. On average, an individual’s gut microbiota is composed of 500–1000 unique bacterial species [5]. More than 95% of microbial species are unable to grow on culture medium; however, the development of DNA-based techniques in the 1980s has led to the discovery of previously unknown microbiota. The two main approaches used for analyzing the microbiome are 16S ribosomal RNA (rRNA) gene amplicons and shotgun metagenomics. The 16S rRNA subunit gene is composed of highly conserved ubiquitous sequences and has regions that varied with greater or lesser frequency during evolution. The 16S rRNA sequencing provides excellent species level identifications but is generally insufficient to identify strain-level differences. Similar gene marker amplicon sequences are clustered as operational taxonomic units (OTUs). In contrast, metagenomic analysis provides an assessment of the functional attributes of the microbiome. The application of high-throughput sequencing has unveiled the enormous diversity, functional and intraindividual stability, interindividual variability, and influence of host genetics and environmental factors shaping microbiome composition [6,7].

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The bacterial genome, defined as the collective genomes of the microbiota, vastly outnumbers the human microbiome and has coevolved with humans to complement activities such as degradation of bile acids [8], synthesis of vitamins and amino acids [9], metabolism of complex polysaccharides [10], maturation of the immune system [11], and degradation of dietary oxalates [12]. Postnatal colonization of the intestine educates our immune system and reduces allergic responses to food and environmental antigens [11]. Studies have shown that individuals living in the same region, belonging to the same family, or having similar diets share similar phylogenetic composition of the gut microbiome [13]. The gut microbiome appears to adapt to the needs of the host, providing the metabolic functions needed to process its diet [14]. It generally remains stable over time. A study characterizing the long-term stability of the human gut microbiota using low error amplicon sequencing of fecal samples from 37 healthy adults collected for over 5 years demonstrated remarkably stable microbiota in individuals and between family members over the follow-up period. These findings emphasize the importance of early gut colonizers acquired from parents and siblings, and their potential life-long effect on our health and disease [15].

In humans the predominant intestinal microbial groups include *Bacteroidetes*, *Firmicutes*, and *Actinobacteria*. Other phyla, such as *Proteobacteria*, *Verrucomicrobia*, *Cyanobacteria*, *Fusobacteria*, *Spirochaetes*, and *TM7* are also present in smaller proportions [16,17]. Each species of bacteria colonizes a different area of the gastrointestinal tract (Table 11.1). Together, gut microbiota and human hosts exist in symbiosis, a state of mutual harmony. Disruption in the intestinal membrane barrier and increased permeability to gut-derived toxins results in endotoxemia-mediated inflammation which has been observed in various chronic diseases, including CKD, metabolic bone disease [22], diabetes [23], obesity [23], nephrolithiasis [24], hypertension [25,26], and cardiovascular disease [27–29].

The Gut Microbiome, Dysbiosis, and CKD

Microbiota and the maintenance of the intestinal epithelial barrier

The intestinal epithelium serves as a dynamic barrier, allowing the absorption of nutrients while also preventing the translocation of antigens and pathogens (Fig. 11.1). A single layer of columnar epithelial cells separates the intestinal lumen from the underlying lamina propria [30]. These epithelial cells are bound together by tight junctions [31]. Commensal bacteria maintain the integrity of the barrier by several mechanisms, including restoration of tight junction protein structure [32], introduction of epithelial heat-shock proteins [33,34], upregulation of mucin genes [35], competition with pathogenic bacteria for binding to epithelial cells [36], and secretion of antimicrobial peptides [37]. The microbiota also protect the epithelial barrier by suppressing intestinal inflammation. Commensal gut bacteria interact with Toll-like receptors (TLRs), a family of pattern-recognition receptors who sense microbial infection through the binding of ligands and then initiate immune defense responses. For example, the

TABLE 11.1 Distribution and composition of the microbiota along the gastrointestinal tract.

Gastrointestinal tract	Healthy population		CKD/ESRD population
	Dominant species	**Microbial number (cells/g)**	**Alterations from normal microbiota**
Stomach	*Lactobacillus*, *Helicobacter*	10^1	
Duodenum	*Staphylococcus*, *Streptococcus*	10^3	Human studies: increased counts (10^6–10^7) [18]
Jejunum	*Enterococcus*, *Streptococcus*, *Lactobacillus*	10^4	Human studies: increased counts (10^6–10^7) [18]
Ileum	*Enterobacteriaceae*, *Bacteroides*, *Clostridium* segmented filamentous bacteria	10^7	
Colon	*Firmicutes*, *Bacteroidetes*, *Actinobacteria*, *Proteobacteria*, *Clostridium*, *Lactobacillaceae*, *Prevotellaceae*, *Fusobacteria*, *TM7*	10^{12}	Human studies: overgrowth of aerobic bacteria (about 100 times) [19], decreased *Bifidobacteria* and higher *Clostridium perfringens* [19], lower species richness [20]. Experimental animal studies: increased *Proteobacteria*, *Enterobacteriaceae*, *Escherichia*, *Enterobacter*, *Acinetobacter*, *Proteus*, and *Proteus* spp., and decreased *Lactobacillus*, *Bifidobacterium* spp. [21], and decreased *Lactobacillaceae* and *Prevotellaceae* [21]

CKD, Chronic kidney disease; *ESRD*, end-stage renal disease.

Adapted from Ramezani A, Raj DS. The gut microbiome, kidney disease, and targeted interventions. J Am Soc Nephrol 2014;25:657–70.

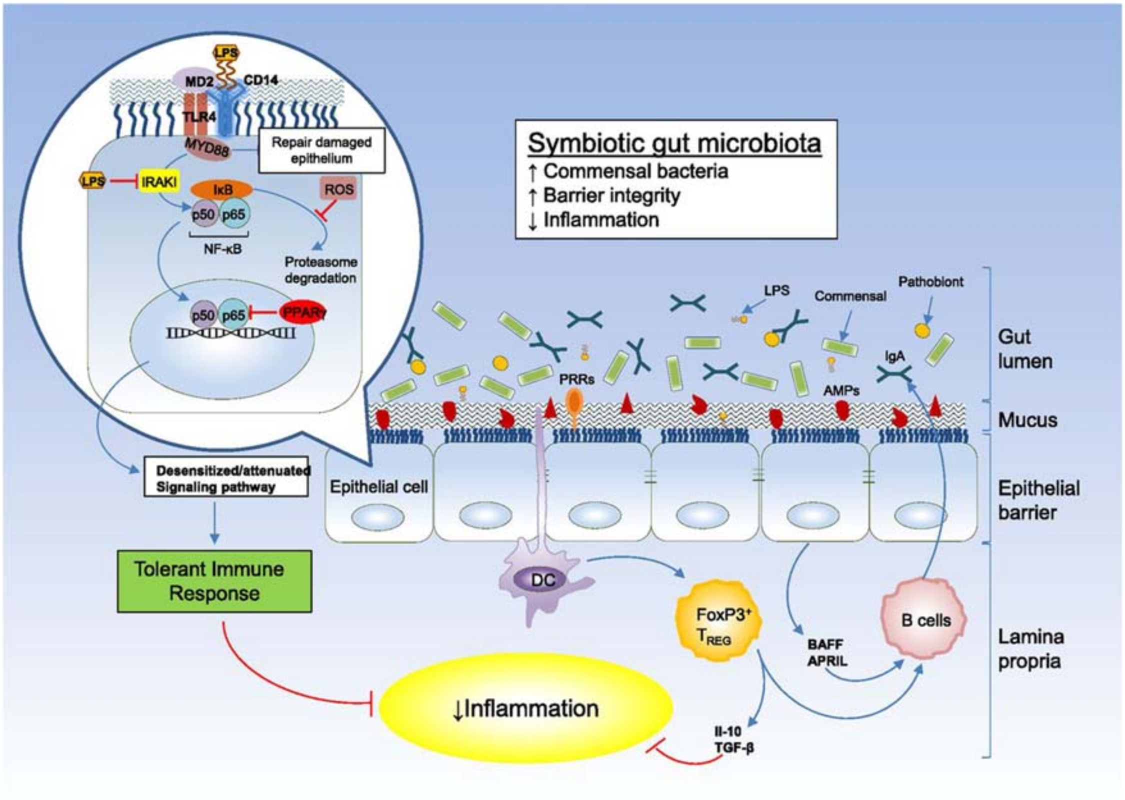
LPS
MD2
CD14
TLR4
MYD88
Repair damaged epithelium
LPS
IRAKI
IκB
ROS
p50
p65
NF-κB
Proteasome degradation
p50
p65
PPARγ
Symbiotic gut microbiota
↑ Commensal bacteria
↑ Barrier integrity
↓ Inflammation
LPS
Commensal
Pathobiont
Gut lumen
IgA
PRRs
AMPs
Mucus
Desensitized/attenuated Signaling pathway
Epithelial cell
Epithelial barrier
Tolerant Immune Response
DC
FoxP3⁺ T_{REG}
B cells
BAFF
APRIL
Lamina propria
↓Inflammation
Il-10
TGF-β

FIGURE 11.1 Intestinal epithelial barrier and inflammatory responses to symbiotic and dysbiotic microbiota. Source: *Adapted from Ramezani A, Raj DS. The gut microbiome, kidney disease, and targeted interventions. J Am Soc Nephrol 2014;25:657–70.*

stimulation of TLR2 promotes B-mediated cell survival via myeloid differentiation factor 88, preserving tight junction assembly against stress-induced damage [38].

Dysbiosis and CKD

Dysbiosis refers to an imbalance in the gut microbial community leading to qualitative and quantitative alterations in its activities [39]. Gut dysbiosis has been associated with several diseases such as obesity [40], type 2 diabetes mellitus [41], inflammatory bowel disease [42], and cardiovascular disease [43–46]. One of the main factors leading to dysbiosis is antibiotic use, which decreases the diversity and relative quantities of bacterial groups even once therapy has completed [47–49]. Diet has a significant impact on the health of the microbiome; for example, fiber intake has been shown to directly interact with gut microbes, leading to the production of beneficial metabolites [50], and ingestion of artificial sweeteners has been shown to negatively impact the composition of the gut microbiota [51]. Several studies have shown that patients with CKD exhibit changes in microbiome composition [20,52,53]. For example, Vaziri et al. found that 190 microbial OTUs differed significantly in abundance between end-stage renal disease (ESRD) patients and healthy controls [20]. Demonstrated factors in dysbiosis in this population include less consumption of fiber [54], iron treatment [55], delayed intestinal transit time [56], antibiotic use, and attenuated protein assimilation [57].

When compared to healthy controls, CKD patients exhibit differences in the colonization of aerobic and anaerobic organisms (Table 11.1). In general, low bacterial diversity, an increase in *Proteobacteria*, *Enterobacteria*, and *Clostridium perfringens*, and a decrease in *Lactobacillus* and *Bifidobacterium* species in the colonic gut have been observed in CKD patients versus healthy controls [58]. The duodenum and jejunum, which are not normally heavily colonized in healthy persons, show greatly increased aerobic (10^6 bacteria/mL) and anaerobic (10^7 bacteria/mL) colonization [18]. Stool microbiome analysis in ESRD patients has shown an increase in bacteria families with urease, *p*-cresyl, and indole-forming enzymes and a reduction in short-chain fatty acid (SCFA)-producing commensals [59]. Other studies comparing ESRD patients to healthy controls have shown a 100-time increase in the number of aerobic bacteria such as *Enterobacteria* and *Enterococci* species in hemodialysis patients [19].

CKD and the gut barrier function

Uremia appears to increase intestinal permeability in both murine models and CKD patients [60,61]. Studies in uremic rats have demonstrated systemic oxidative stress, azotemia, and marked depletion of key protein components of the epithelial tight junction (claudin 1, occludin, ZO1) in the stomach, jejunum, and ileum [62]. They have also shown penetration of bacteria across the intestinal wall and into the mesenteric lymph nodes [21,63]. These disruptions can lead to chronic damage to the gut barrier. Autopsy studies of hemodialysis patients have revealed decrease in villous height, inflammation in the intestinal lamina propria, liver fibrosis, and signs of cardiovascular disease [63].

Uremic toxins and CKD

Uremic toxins are generated from protein metabolism and adversely affect biologic functions (Fig. 11.2). In 1965 Einhheber and Carter demonstrated that germfree anephric mice survived longer than anephric mice with an intact gut microbiome [64]. Similarly, a study of dialysis patients with and without colons showed that these toxins were minimal or absent in patients without colons [65]. The intestinal origin of uremic toxins has been demonstrated in several studies. For example, protein catabolism generates ammonia, which is converted into urea via the ornithine–urea cycle. While mammals cannot metabolize urea, gut bacteria expressing the enzyme urease can cleave urea into ammonia and carbon dioxide [66]. Some of this ammonia can then be used for the synthesis of amino acids by the microbes or can enter the host circulation [67]. Ammonia can also be generated by microbial fermentation of the amino acids glutamine, serine, threonine, and glycine. In high levels, ammonia and urea are toxic to cells and have been shown to disrupt the intestinal barrier functions and epithelial tight junctions [68–70]. Gut microbes have been shown to generate other uremic toxins such as *p*-cresol, phenol, and indole through the fermentation of the amino acids phenylalanine, tyrosine, and tryptophan [71].

Of note, uremic toxins are difficult to remove via hemodialysis as they are largely protein-bound, and metabolism of phenols and aromatics may be affected by antibiotic use [72]. Important uremic toxins, as well as their related bacteria and pathogenic mechanisms, are described in Table 11.2. The following sections highlight gut-derived metabolites that have strong associations with CKD, cardiovascular disease, and other chronic conditions.

Indoxyl sulfate

Indoles are an aromatic group of compounds containing a pyrrole ring. Bacterial metabolism of

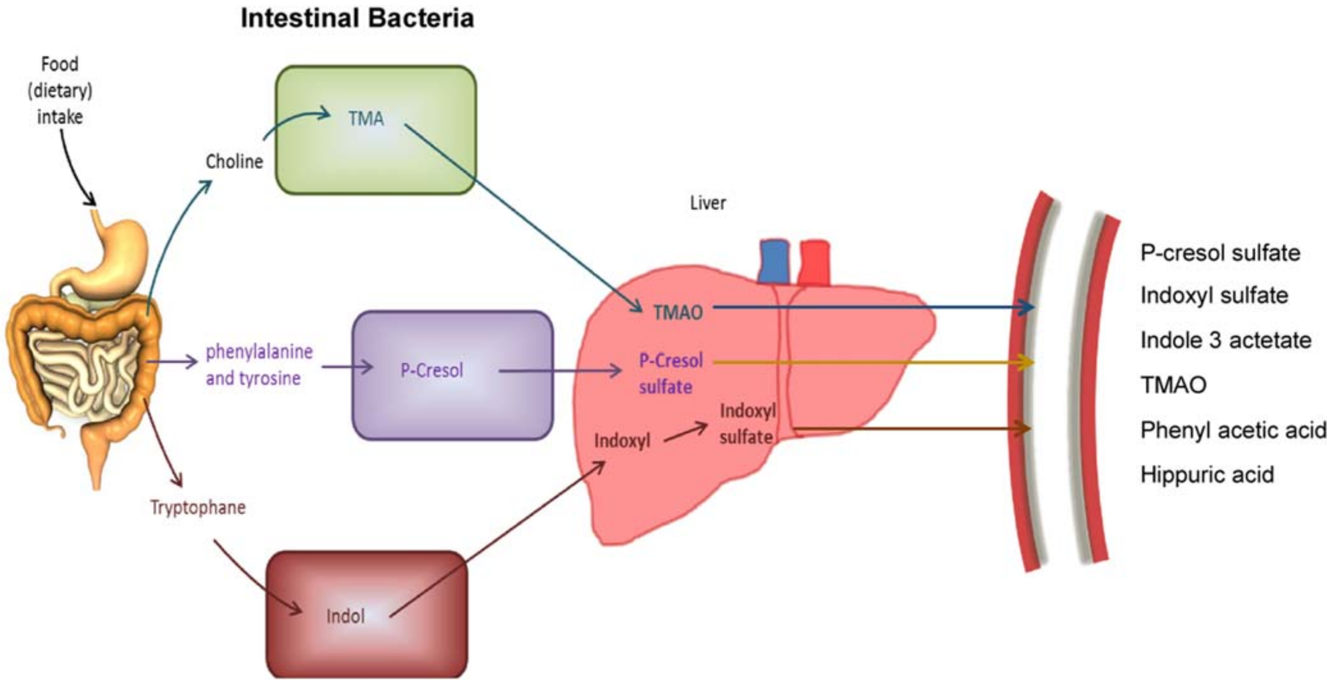

FIGURE 11.2 Schematic showing some of the major toxic metabolites originating from synthesis by dysbiotic gut microbiome and potential pathways linking their accumulations to pathophysiological consequences in CKD. Source: *Adapted from Ramezani et al., Role of the Gut Microbiome in Uremia: A Potential Therapeutic Target, AJKD (Elsevier) 2016;67(3):483–98.*

TABLE 11.2 Gut microbiome–derived uremic toxins.

Group	Solute	Source	Related bacteria	Mechanism of disease	References
Carbamide	Ammonia and urea	Ammonia, the end product of protein catabolism, is converted to urea by ornithine–urea cycle. Gut bacteria expressing urease cleave urea into ammonia and carbon dioxide	Urease is produced by several bacterial species, including *Clostridium* spp., *Enterococcus*, *Shigella*, and *Escherichia coli*	High concentration of ammonia changes the luminal pH causing uremic enterocolitis; amino acid catabolism leads to the formation of sulfides, phenolic compounds, and amines, which are inflammatory and/or precursors to the formation of carcinogens	[7,66,67]
Guanidine	Creatinine, guanidine, and uric acid	Colonic bacteria degrade creatinine in gut. Guanidine is produced by creatinine metabolism via *Pseudomonas stutzeri*. Intestinal organisms can degrade urate, generating allantoin, allantoic acid, urea, and ammonia		Guanidine accumulation in CKD increases mortality as shown in animal studies	[73–77]
Guanidine	1-Methylguanidine	Metabolism of creatinine	*P. stutzeri*	Accumulates in CKD and is considered a uremic toxin; administration to rats with kidney failure demonstrated a dose-dependent increase in mortality	[78–80]
Amine	TMAO	Endogenous generation; bacterial metabolism of dietary lipid phosphatidylcholine, carnitine, and choline	*Order Clostridiales* and genus *Ruminococcus*	Increases the progression of renal disease and mortality in CKD; increases tubulointerstitial fibrosis and collagen deposition; increases phosphorylation of Smad3, which regulates the profibrotic transforming growth factor-β/Smad3 signaling	[81–83]
Amino acid	Homocysteine	Endogenous generation; intestinal bacteria lower homocysteine by production of folic acid	*Bifidobacterium* spp.	Increases risk of Cardiovascular Disease (CVD) and death; increases oxidative stress (through the production of reactive oxygen species), binds to nitric oxide, produces homocysteinylated proteins, and leads to the accumulation of its precursor, *S*-adenosylhomocysteine, a potent inhibitor of biological transmethylations	[84]
D-Amino acid	D-Lactic acid	Ingestion; endogenous generation, and bacterial production	*Enterococcus* and *Streptococcus* spp.	Involved in D-lactic acidosis; associated with neurotoxic effects and encephalopathic symptoms	[18,85]
Dicarboxylic acid	Oxalate	Ingestion and endogenous generation, certain intestinal bacteria have oxalate degrading potency to remove oxalate	*Oxalobacter formigenes*, *Bifidobacterium lactis*, *Enterococcus faecalis*, and *Eubacterium lentum*	Hyperoxaluria leads to urolithiasis; increased endothelial cell replication and migration leading to atherosclerosis	[86]
Phenol	*p*-Cresol sulfate	Bacterial metabolism of tyrosine and phenylalanine	*Clostidium difficile*, *Faecalibacterium prausnitzii*, *Bifidobacterium*, *Subdoligranulum*, *Lactobacillus*	Increases progression of CKD, CVD, and mortality in hemodialysis patients; decreased cytokine-stimulated expression of endothelial adhesion molecules; increases endothelial permeability	[87–89]
Indole	Indoxyl sulfate	Bacterial metabolism of tryptophan	*Clostridium sporogenes*, *E. coli*	Increases vascular stiffness, aortic calcification, and cardiovascular mortality; increases oxidative stress in endothelial cells; increases vascular smooth muscle cell proliferation; increases expression of genes related to tubulointerstitial	[90–95]

(*Continued*)

TABLE 11.2 (Continued)

Group	Solute	Source	Related bacteria	Mechanism of disease	References
				fibrosis; associated with nephrotoxicity	
Monocarboxylic acid	Indole-3-acetic acid	Endogenous; bacterial metabolism of tryptophan	*C. sporogenes*, *Clostridium bartlettii*, *E. coli*	Induce glomerular sclerosis and interstitial fibrosis in subtotally nephrectomized rats, thus contributing to the progression of CKD; serum Indole-3-Acetic Acid (IAA) is a significant predictor of mortality and cardiovascular events in patients with CKD; induces proinflammatory enzyme cyclooxygenase-2 and oxidative stress	[96,97]
Monocarboxylic acid	Phenylacetic acid	Endogenous; bacterial metabolism of phenylalanine and tryptophan	*Clostridium* spp., *Bacteroides* spp.	Toxic; induces nausea, vomiting, diarrhea, and convulsion; associated with impaired immunoregulation, increased oxidative stress, and osteoblast dysfunction; shown to causes renal tubular damage in dogs	[98–101]
Carboxylic acid	Hippuric acid	Ingestion, bacterial metabolism of aromatic compounds and polyphenols	*Clostridia* spp.	Nontoxic; ↑the anion gap acidosis; may cause glucose intolerance and interfere with erythropoiesis and platelet cyclo-oxygenase activity	[102–104]
Polyamines	Polyamines	Many polyamines are generated by microbiota from precursor amino acids		Polyamines play a role in the lack of tissue responses to hormones in uremia. Associated with erythropoietin inhibition, anemia of CKD	[101,104]

CKD, Chronic kidney disease; *TMAO*, trimethylamine *N*-oxide.

tryptophan generates more than 600 indoles in the gut, which are then absorbed and conjugated with sulfate by the liver [105]. Indoxyl sulfate (IS) is an indole that is highly protein-bound and associated with CKD progression, cardiovascular disease, and low-turnover bone disease [106,107]. IS is normally cleared by the proximal tubules of the kidneys and is transported via organic anion transports 1 and 3 (OAT1 and OAT3). In experimental models of kidney failure, OAT1 and OAT3 expression is reduced [108], leading to the buildup of IS in proximal tubular cells [109]. Accumulation of IS in proximal tubular cells has been associated with the activation of NF-kB and plasminogen activator inhibitor type 1 expression [109,110]. Following administration to uremic rats, IS also increases gene expression of transforming growth factor beta-1 (TGF$_B$1) and tissue inhibitor of metalloproteinase, both of which mediate tubulointerstitial fibrosis [111].

IS is also associated with increase all cause and cardiovascular mortality in CKD patients, as well as increased aortic calcification and vascular stiffness [112–114]. Investigational studies have demonstrated that IS induces vascular smooth muscle cell proliferation [90], attenuates endothelial cell repair mechanisms [114], increases oxidative stress in endothelial cells [114], and enhances shedding of endothelial microparticles [115]. IS appears to disrupt oxygen sensing in erythropoietin producing cells, decreasing erythropoietin production [116]. Furthermore, IS affects bone health in a myriad of ways; it is taken up by osteoblasts, increases oxidative stress, decreases parathyroid hormone receptor expression, and inhibits osteoclast function [117,118].

p-Cresol sulfate

p-Cresol sulfate (also called *p*-cresyl sulfate or PCS) is a uremic retention solute and toxin which depends on tubular secretion via specific transporters for excretion out of the kidney [91,92,96,119,120]. It accumulates in CKD, leading to progressive renal disease through activation of the TGF/SMAD pathway, activation of the intrarenal renin angiotensin system, and possibly epithelial mesenchymal transformation causing renal fibrosis [121]. In a study of nephrectomized rats, administration of PCS caused significant renal tubular damage in 5/6 rats by increasing oxidative stress and inflammatory cytokines [82]. PCS is also associated

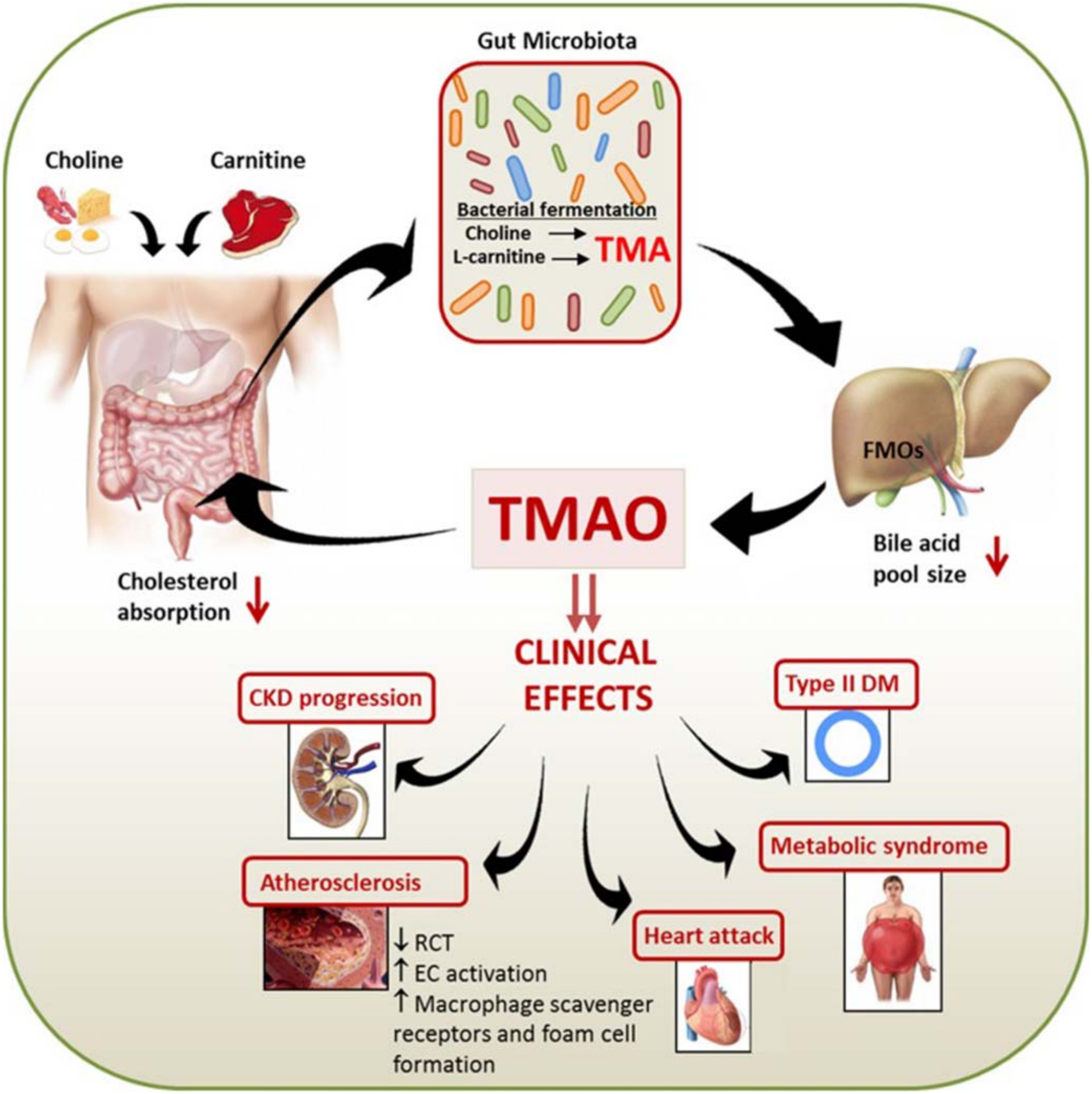
Gut Microbiota
Choline
Carnitine
Bacterial fermentation
Choline → TMA
L-carnitine → TMA
FMOs
TMAO
Cholesterol absorption ↓
Bile acid pool size ↓
CLINICAL EFFECTS
CKD progression
Type II DM
Atherosclerosis
Metabolic syndrome
Heart attack
↓ RCT
↑ EC activation
↑ Macrophage scavenger receptors and foam cell formation

FIGURE 11.3 Schematic representation of the link between diet, gut microbiota, TMAO and the clinical manifestations of this uremic toxin. Source: *Adapted from Velasquez et al. Trimethylamine* N-*oxide: the good, the bad and the unknown. Toxins (Basel) 2016;8(11).*

with cardiovascular disease and increased all-cause mortality in CKD and ESRD patients [122–124], as well as insulin resistance and cachexia [125].

Trimethylamine N-oxide

Trimethylamine *N*-oxide (TMAO) is a metabolite generated from gut microbial degradation of choline, betaine, and carnitine. Carnitine is a metabolite found in red meat. Microbial enzymes transform choline and L-carnitine into trimethylamine (TMA), a volatile gas, which then travels to the liver via the portal circulation, where it is transformed into TMAO [126] (Fig. 11.3). In a landmark study, Wang et al. screened more than 2000 metabolites in 75 patients with cardiovascular disease, identifying an association between the metabolites TMAO, choline, and betaine and heart disease [44]. Elevated TMAO levels are a predictor of increased long-term mortality in patients with congestive heart failure independent of traditional risk factors [127]. How TMAO promotes atherosclerosis remains elusive; proposed mechanisms include alteration of cholesterol and sterol metabolism, promotion of foam cell formation, and alterations in bile acid metabolism and sterol transporters in the liver and intestine [44,128].

Patients with CKD have an elevated level of TMAO and these increased levels are associated with increased risk of death. In animal models, ingestion of TMAO and choline was associated with signification increase in SMAD3 phosphorylation and led to tubulointerstitial fibrosis and collagen deposition [128].

Endotoxin

Endotoxin is a phospholipid that forms the outer membrane of most Gram-negative bacteria. Circulating endotoxin binds lipopolysaccharide-binding protein, forming a complex that interacts with the MD-2 part of TLR4, anchored by the CD14 receptor [129]. Binding of CD14 stimulates activation of NF-kB as well as the production of inflammatory cytokines [130]. It has been proposed that endotoxin translocation from the gut is one of the causes of inflammation in CKD. Studies have demonstrated that soluble CD14 is associated with CKD progression, Cardiovascular Disease (CVD), and mortality in patients with kidney disease [131−133]. Endotoxin has also been implicated in the pathogenesis of atherosclerosis by mediating endothelial cell injury, boosting recruitment of monocytes, transforming macrophages to foam cells, and activating coagulant activity [134,135]. Additionally, murine models have shown that endotoxin may be a trigger of insulin resistance, obesity, and diabetes [136].

Short-chain fatty acids

Dysbiosis can also lead to decreased production of beneficial metabolites, such as SCFA. SCFAs are 1- to 6-carbon aliphatic organic acids generated by gut anaerobic fermentation of dietary polysaccharides. SCFAs include acetate, propionate, and butyrate, which can enter the systemic circulation via passive diffusion and active transport through colonocyte cells. Butyrate is the primary source of energy for colonocytes and is thought to be integral to maintaining the health of the intestinal epithelium. SCFAs affect a range of host functions, including gut motility, immune regulation, energy metabolism, and blood pressure regulation, through the activation of G protein−coupled receptors [137]. In a germ-free mouse model, treatment with SCFA reduced ischemia reperfusion injury and, thus, SCFA may be an important mediator of acute kidney injury [138,139].

Gut microbiome and hypertension

Dietary salt intake, antibiotic use, regulation of serotonin and norepinephrine, renal sodium excretion, and metabolites such as TMAO are all known to influence the development of hypertension via the modulation of the gut microbiota. Animal studies have supported a causal effect of gut microbiota on blood pressure [140]. For example, normotensive rats developed hypertension following the transplantation of fecal contents from hypertensive rats [141]. Gut microbiome analysis of participants of the CARDIA study (Coronary Artery Risk Development in Young Adults) showed inverse association of hypertension with bacterial richness (alpha diversity) and several genera associated with hypertension [142]. Other studies have conclusively shown depletion of *Lactobacillus* species, particularly *Lactobacillus murinus*, with high-salt diet consumption with resultant hypertension. Daily treatment with *L. murinus* was shown to prevent high-salt diet-induced generation of T_H17 cells and consequently ameliorate salt-sensitive hypertension [25].

SCFA produced by the gut microbiota activate two orphan G protein−coupled receptors, GPR41 and GPR43, and olfactory receptor 78 (Olfr78) [26]. The increase in blood pressure caused by SCFA-induced renin release from the afferent arteriole is mediated by Olfr78 [26]. This, in turn, can be counteracted by the vasodilatory action of GPR43 [26].

Targeted interventions to treat dysbiosis in CKD/ESRD

Several targeted interventions to reestablish intestinal symbiosis, neutralize bacterial endotoxins, or adsorb gut-derived uremic toxins have been developed. Human and animal studies suggest that prebiotics, synbiotics, and probiotics as well as dietary modifications may have therapeutic roles in maintaining metabolically balanced gut microbiota, as well as attenuating the progression of CKD and uremia-associated complications [143].

Prebiotics

A prebiotic is a substrate that is metabolized by selected beneficial host microorganisms [144]. While this definition applies to body sites outside of the gastrointestinal tract and to diverse categories other than food, most studies have been done using prebiotic foods such as inulin, fructo-oligosaccharides, galacto-oligosaccharides, soya-oligosaccharides, xylo-oligosaccharides, and pyrodextrins which nourish the gut microbiota. Many prebiotics promote the growth of *Bifidobacteria* in the gut, improving gut health and reducing inflammatory diseases [145]. The use of prebiotics in the form of fermentable fibers in CKD patients has been shown to reduce serum urea nitrogen while increasing fecal nitrogen content [146,147]. In contrast, Poesen et al. used prebiotic arabinoxylan oligosaccharide in nondialysis CKD patients and found no significant effects on uremic solutes [148]. Further research must be done to clarify the role of prebiotics in reducing uremic toxins.

Probiotics

The World Health Organization defines probiotics as "live microorganisms which when administered in adequate amounts confer a health benefit on the host" [149]. Unlike prebiotics, which stimulate the growth of host's own beneficial microbes, probiotics are directly supplemented beneficial bacteria commonly in the form of *Lactobacillus* and *Bifidobacterium* [150]. Several studies have demonstrated that probiotic use can decrease the level of uremic toxins and improve renal survival. A placebo-controlled blinded study in nephrectomized rats randomized to different probiotic regimens showed improvement in uremic toxins, renal function, and survival in rats who received *Bacillus pasteurii* or *Sporolac* regimens [151]. *Lactobacillus acidophilus* use in hemodialysis patients has been associated with reduction in the gut uremic toxins dimethylamine and nitrosodimethylamine [18]. *Bifidobacterium longum* has been associated with delay of ESRD in late-stage CKD patients as well as reduction of IS levels in hemodialysis patients [152,153]. A 6-month prospective multicentric trial conducted in stages 3 and 4 CKD patients using a probiotic mixture of *L. acidophilus*, *B. longum*, and *Streptococcus thermophilus* showed an improvement in BUN and uric acid levels, with approximately half of the patients demonstrating an improvement in creatinine levels and overall improvement in quality of life and well-being [154]. Wang et al. conducted a randomized clinical trial in peritoneal dialysis patients with a probiotic capsule containing *Bifidobacterium bifidum*, *Bifidobacterium catenulatum*, *B. longum*, and *Lactobacillus plantarum* strains for 6 months compared with placebo. A reduction in serum endotoxin levels and certain proinflammatory cytokines as well as preservation of residual renal function was observed in the probiotic group [155]. The use of *Lactobacillus* and *Bifidobacterium* in hemodialysis patients has shown beneficial effects on glucose homeostasis and reduction in inflammation in diabetics [156]. In contrast, a trial of a probiotic containing *S. thermophilus*, *L. acidophilus*, and *B. longum* in another cohort of hemodialysis failed to reduce uremic toxins and inflammatory markers when compared to placebo [157].

Archaea are unicellular microorganisms that were initially thought to be present only in extreme climates. The archaea present in humans are strict anaerobes, predominantly methanogenic, and use TMA as their substrate for growth. Ramezani et al. screened for the colonization potential and TMAO-lowering efficacy of five methanogenic archaea species in C57BL/6 mice fed with high-choline/TMA-supplemented diet and noted that all five species could colonize the mice and lower plasma TMAO levels [158]. Probiotic use remains an active area of interest for the management of CKD and its complications.

Symbiotics

Symbiotics refer to a combination of prebiotics and probiotics. Guida et al. compared the use of a symbiotic containing inulin, *Lactobacillus*, and *Bifidobacterium* strains to a placebo in CKD 3 and 4 patients and found lower levels of *p*-cresol in the symbiotic group compared to placebo after 1 month [159]. Another randomized study in CKD 3 and 4 patients over 6 weeks showed a reduction in serum nitrogen levels without significant effect on renal function [160]. Rossi et al. used symbiotics in predialysis patients and found lower levels of *p*-cresol without significant lowering of IS. There was increase in albuminuria in the symbiotic arm without any significant difference in renal outcomes [161]. In hemodialysis patients, increase in stool *Bifidobacterium* counts with subsequent improvement in gastrointestinal symptoms has been reported [162,163].

Other therapies

Other compounds have also been shown to affect the gut microbiome. Sevelamer, a phosphorus binder, has shown to bind endotoxins and has been associated with reduced endotoxin and CD14 levels but appears to have no significant effects on uremic toxins [164−166]. In small studies, oral adsorbent AST-120, an oral sorbent, adsorbs urea-derived ammonia and has been associated with lower plasma IS levels as well as decreased disruption of intestinal epithelial membrane [167,168]. However, larger randomized trials have not shown convincing benefits except for possible mild decrease in progression to dialysis [169]. E5564, a synthetic analog of lipopolysaccharide, has been shown to reduce adverse effects and inflammation arising from endotoxins by blocking the activity of lipopolysacchararide (LPS) in healthy subjects [170,171]. AT-1001, an inhibitor of paracellular intestinal permeability, has been associated with reduced intestinal barrier dysfunction, inflammation, and gastrointestinal symptoms in celiac disease patients [172].

Dietary modifications and fecal transplantation

Several studies have demonstrated the beneficial role of dietary fiber (plant-derived nondigestible carbohydrates) in maintaining gut symbiosis in healthy patients. Fibers increase lactic acid bacteria, such as *Ruminococcus*, *Eubacterium rectale*, and *Roseburia*, and reduce *Clostridium* and *Enterococcus* species [173]. In CKD patients, high dietary fiber consumption has been associated with lower levels of C-reactive protein and lower inflammation and mortality in patients with CKD [54,174]. A study in hemodialysis patients showed that increased dietary fiber intake reduced plasma-free levels of IS and *p*-cresol [175].

There is growing interest on the impact of vegetarian, vegan, and plant-based diets on gut microbiome and overall health, as they are high in dietary fibers as well as polyphenols, which increase the beneficial bacteria *Bifidobacteria* and *Lactobacillus* and provide antiinflammatory effects and cardiovascular protection [175]. Adherence to plant-based diets has been associated with favorable kidney disease outcomes, but more studies are needed to investigate the connection between plant-based diets, the gut microbiome, and CKD progression [176].

Fecal microbiota transplantation has improved bacterial diversity and demonstrated efficacy against *Clostridium difficile* colitis but no trials have been conducted in CKD [177,178].

Microbiome engineering

Microbes can be engineered into "smart" living therapeutic agents programed to produce a continuous and inexpensive supply of heterologous molecules of biomedical interest that could be used in the treatment of myriad of diseases [179]. For example, bacterial tryptophanases convert tryptophan to indole, which is then absorbed and modified by the host to produce IS. Devlin et al. found that in the majority of individuals, the genus *Bacteroides* has the most abundant tryptophanases in the gut microbiome. In a series of in vitro and animal studies, they showed that deleting this gene eliminates the production of indole in vitro, and that alteration of gene expression of tryptophanase as well as reduction of *Bacteroides* lower generation of IS [180].

In the intestine, bacterial urease converts host-derived urea to ammonia and carbon dioxide. Shen et al. showed that animals inoculated with altered *Schaedler flora* (a defined consortium of eight bacteria with minimal urease gene content) resulted in a persistent reduction in fecal urease activity and ammonia production [181].

Conclusion and future directions

In summary the gut microbiome vastly outnumbers the human genome and has a symbiotic relationship with its host, performing various nutritional, metabolic, and immune functions. An altered bacterial flora is termed dysbiosis. Gut dysbiosis is associated with the degradation of the intestinal membrane, as well as increased intestinal permeability and translocation of gut-derived uremic toxins into the blood. This results in inflammation, CKD progression, and worsening of various metabolic diseases. In CKD, uremia, as well as factors such as constipation and antibiotic use, leads to further dysbiosis and accumulation of uremic toxins. Uremic toxins such as IS and PCS are associated with CKD progression, CVD, bone disease, and inflammatory diseases. Use of prebiotics, probiotics, and symbiotics has been attempted to restore symbiosis of gut flora and has shown inconclusive results. High fiber and plant-based diets may also be beneficial to the gut microbiome, but more research is needed in patients with CKD. Targeted interventions on the gut microbiome may potentially halt the progression of kidney diseases as well as cardiovascular and metabolic diseases.

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PART II

Treatment of altered metabolism in chronic kidney disease

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CHAPTER

12

Assessment and risk factors for protein-energy wasting and frailty in chronic kidney disease

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Introduction

Protein-energy wasting (PEW) and frailty are complex, overlapping, and interconnected geriatric syndromes (Fig. 12.1). Both are associated with unfavorable outcomes in the chronic kidney disease (CKD) and non-CKD populations and early diagnosis is critical to intervening effectively. Although both PEW and frailty have become more recognized recently, they are underdiagnosed partly due to the lack of a single definition for each and a scarcity of diagnostic tools that can be utilized in clinical practice.

In this chapter, we will focus on assessing the components of the diagnostic criteria of PEW and frailty in CKD patients. The risk factors of these syndromes will also be discussed.

Assessment for protein-energy wasting

PEW is a state of decreased body reserve of protein and energy [1]. Frailty is one of the geriatric syndromes of poor functional status or physical reserve as a result of worsening multiple organ functions, which leads to poor health consequences [2–4]. Frailty and PEW are interconnected and share several contributing factors, especially among CKD patients (Fig. 12.1). Methods to assess for and diagnose each condition can help to plan for interventions, improve prognostication, and clarify further research goals.

Diagnosis of protein-energy wasting

Given the heterogeneity of definitions for PEW, the International Society of Renal Nutrition and Metabolism committee proposed the definitions and criteria for the diagnosis of PEW. Abnormalities of nutrition-related laboratories, body composition, and dietary intake are used for the diagnosis of PEW, with at least three of the four abnormalities needed to diagnose PEW (Table 12.1) [1]. However, protein and energy-wasting may occur separately in the absence of a confirmed diagnosis of PEW [1].

The information and criteria needed to diagnose PEW can mostly be obtained by physical examination and routine laboratory data; however, some criteria are not routinely done in clinical practice limiting the generalizability and adoption of widespread PEW assessments, especially among CKD patients where this information may prove useful for prognostication and counseling regarding possible anticipated outcomes.

Nutrition status can be assessed through both anthropomorphic and nonanthropomorphic measurements, all

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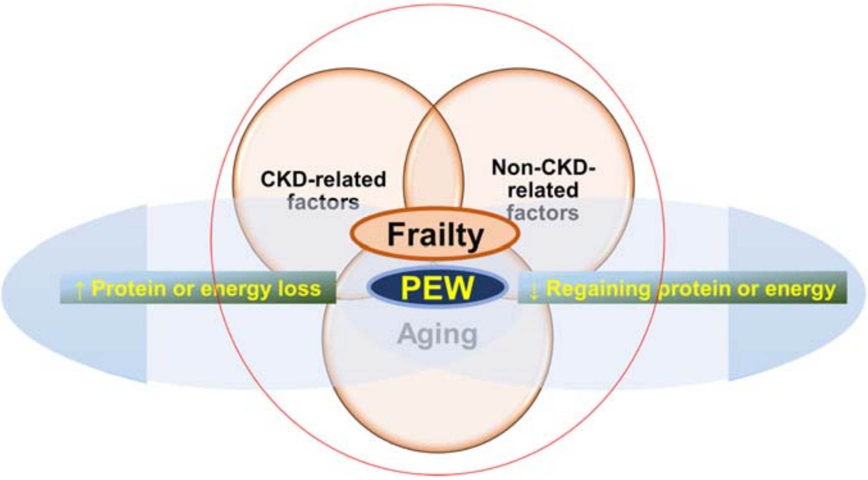

FIGURE 12.1 Interconnection between PEW and frailty. *CKD*, Chronic kidney disease; *PEW*, protein-energy wasting.

TABLE 12.1 Diagnostic criteria for protein-energy wasting by the International Society of Renal Nutrition and Metabolism [1].

Criteria	Definitions	Comments
1. Nutrition-related laboratory abnormalities	• Serum albumin <3.8 g/100 mL • Serum prealbumin (transthyretin) <30 mg/100 mL (for maintenance dialysis patients only; levels may vary according to GFR level for patients with CKD stages 2–5) • Serum cholesterol <100 mg/100 mL	• 3.8 g/100 mL is the value when albumin is measured by bromocresol green
2. Decreased body mass	• BMI <23 kg/m^2 • Unintentional weight loss over time: 5% over 3 months or 10% over 6 months • Total body fat percentage <10%	
3. Low muscle mass	• Muscle wasting: reduced muscle mass 5% over 3 months or 10% over 6 months • Reduced midarm muscle circumference area (reduction >10% in relation to 50th percentile of reference population) • Creatinine appearance	
4. Poor dietary intake	• Unintentional or involuntary low DPI < 0.80 g/kg/d for at least 2 months for chronic dialysis patients or <0.55 g/kg/d for patients with stage 2–5 CKD • Unintentional low DEI < 25 kcal/kg/d 1 for at least 2 months	• DPI and DEI can be assessed by dietary diaries and interviews, or for protein intake by calculation of nPNA or nPCR as determined by urea kinetic measurements

BMI, Body mass index; *CKD*, chronic kidney disease; *DEI*, dietary energy intake; *DPI*, dietary protein intake; *GFR*, glomerular filtration rate; *nPCR*, normalized protein catabolic rate; *nPNA*, normalized protein nitrogen appearance.

of which have their strengths and limitations. Routine clinical and laboratory measurements such as body mass measurements and biochemical markers are easily obtained in most clinical settings. However, the common laboratory variables of albumin, prealbumin, creatinine, and cholesterol can be affected by the presence of inflammation or liver disease, necessitating caution when interpreting nutrition status solely based upon these values alone. Other measurements of muscle mass such as computed tomography (CT) scans, creatinine kinetics, and midarm muscle circumference (MAMC) are not routinely done and may exposure patients to unnecessary radiation. Additionally, dietary intake recalls are typically time-consuming and hand-grip measurements rely on specialized instruments not readily available in most clinical settings.

Body composition can also be ascertained directly through dual-energy X-ray absorptiometry (DXA) (Table 12.2). However, while DXA remains the gold standard in body composition measurements, it is labor intensive, invasive, expensive, increases potentially unnecessary radiation exposure, requires specialized

TABLE 12.2 Direct and indirect methods for body composition measurement for anthropometry to assess nutritional status in chronic kidney disease (CKD) and end-stage kidney disease patients.

	Body composition measurement for anthropometry	
	Direct measurement	**Indirect measurement**
Methods	• Weight • BMI • BIA • NIR • DXA	• Body mass ◦ Weight, BMI ◦ Total body fat percent (SKF, BIA) ◦ Waist circumference ◦ WHR • Muscle mass ◦ Midarm muscle circumference ◦ Creatinine kinetics ◦ NIR ◦ Abdominal CT scan at the L3 vertebral level
Advantages	• Gold standards	• Practical—easy and inexpensive to use • Noninvasive techniques • Some require simple equipment
Disadvantages	• Labor intensive • Expensive • Influenced by a number of CKD-related factors, for example, hydration status • X-ray exposure (although very small = 0.1 time of chest X-ray radiation exposure) • Specialized equipment not readily available everywhere	• Interfered with several factors in CKD • Specialized equipment (MF-BIA, SKF) • Expensive (BIA) • Influenced by a number of CKD-related factors; for example, hydration status

BMI, Body mass index; *CT*, computed tomography; *DXA*, dual-energy X-ray absorptiometry; *MF-BIA*, multifrequency bioelectrical impedance analysis; *NIR*, near-infrared interactance; *SKF*, skinfold thickness; *WHR*, waist-to-hip ratio.

equipment not available at all centers, and is potentially influenced by several CKD-related factors such as hydration status. Indirect measurements of body composition can be done in routine clinical practice, including ascertaining body mass, size, shape, and levels of fatness and leanness by measuring height, weight, skinfolds, and circumferences. More technical and precise measurements with bioelectrical impedance analysis (BIA), creatinine kinetics, and near-infrared interactance (NIR) are not as readily available currently, but likely will increase in prevalence with increasing availability and lower cost of these devices in the future (Table 12.2; Fig. 12.2) [5].

Serum biochemical markers of nutrition

Serum albumin

Several epidemiological studies have consistently shown the association between low serum albumin and mortality in end-stage kidney disease (ESKD) [6–10] and hospitalizations [5].

There is also a negatively graded association between serum albumin and CKD progression to ESKD in diabetic CKD patients [11]; however, there are several factors that affect serum albumin (Table 12.3).

In addition to poor nutrition intakes such as from uremic symptoms and inadequate dialysis, hypoalbuminemia can result from decreased synthesis, increased utilization, and exogenous losses. Conditions leading to decreased synthesis commonly seen in hemodialysis (HD) patients include protein-calorie malnutrition, inflammation, illness, liver failure, or increase muscle catabolism. Increased utilization can be from an increased fractional catabolic rate. Exogenous albumin loss can be via urine or dialysate. Hypoalbuminemia is common among peritoneal dialysis (PD) patients due to plasma volume expansion [5,13].

Although hypoalbuminemia is associated with poor kidney and mortality outcomes, a recent observational study found that stage 5 CKD patients with low serum albumin and elevated high-sensitive C-reactive protein (hsCRP) had a greater mortality risk than those with low serum albumin levels but normal hsCRP [14]. Therefore hypoalbuminemia may be a marker of inflammation in the uremic milieu potentially clouding the ability to diagnose PEW [15–18].

Since serum albumin is influenced by several nonnutritional factors, especially inflammation, we do not recommend its use in isolation to assess nutritional status. Instead, it should be used as a screening tool or incorporated with other tests to assess nutritional status [5].

Serum prealbumin (transthyretin)

Serum prealbumin is a protein synthesized by the liver with a more rapid rate of hepatic synthesis and a more reliable catabolic rate than serum albumin [19]. It circulates with a short half-life and is a relatively sensitive marker for altered nutritional status [5,20]. Similar to serum albumin, low prealbumin levels are associated with higher mortality risk and risk of hospitalization in ESKD patients [21].

Prealbumin in ESKD patients has been positively correlated with normalized protein catabolic rate (nPCR), a marker of nutrition and protein intake, and negatively correlated with inflammatory markers such as interleukin 6 [22]. In combination with serum albumin levels, prealbumin levels are a helpful tool to

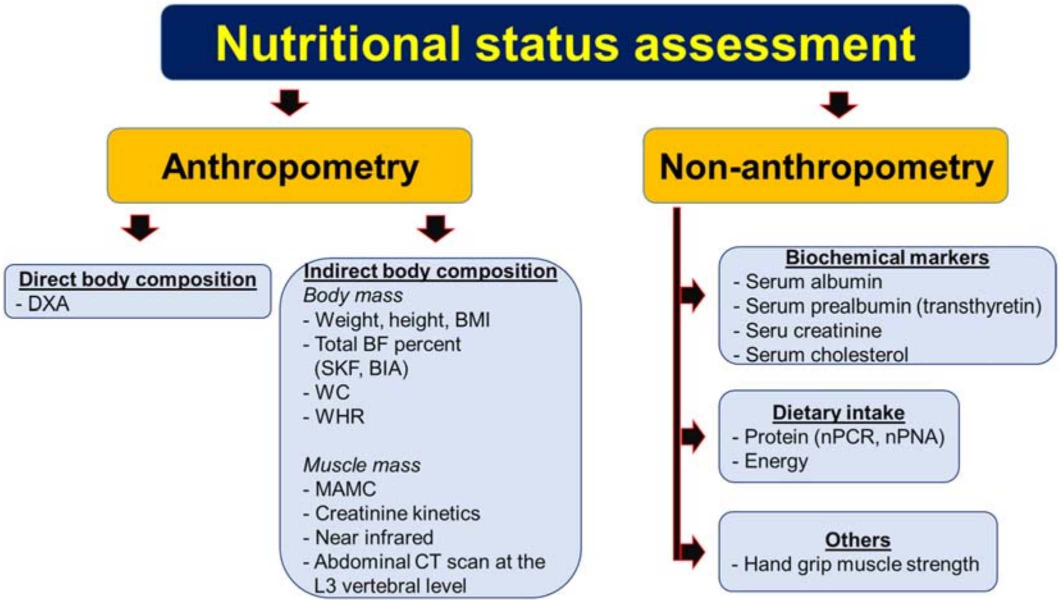
Nutritional status assessment
Anthropometry
Non-anthropometry
Direct body composition
- DXA
Indirect body composition
Body mass
- Weight, height, BMI
- Total BF percent (SKF, BIA)
- WC
- WHR
Muscle mass
- MAMC
- Creatinine kinetics
- Near infrared
- Abdominal CT scan at the L3 vertebral level
Biochemical markers
- Serum albumin
- Serum prealbumin (transthyretin)
- Seru creatinine
- Serum cholesterol
Dietary intake
- Protein (nPCR, nPNA)
- Energy
Others
- Hand grip muscle strength

FIGURE 12.2 Overview methods for nutritional assessments. *BF*, Body fat; *BIA*, bioelectrical impedance analysis; *BMI*, body mass index; *DXA*, dual-energy X-ray absorptiometry; *L*, lumbar; *MAMC*, midarm muscle circumference; *nPCR*, normalized protein catabolic rate; *nPNA*, normalized protein nitrogen appearance; *SKF*, skinfold thickness; *WHR*, waist-to-hip ratio; *WC*, waist circumference.

TABLE 12.3 Common conditions affecting serum albumin in chronic kidney disease (CKD) and end-stage kidney disease patients.

Conditions	Examples	At-risk populations
Increased body water Redistribution of albumin	• Plasma volume expansion • Overhydration [12] • Polytrauma	Advanced CKD, HD, PD patients
Decreased albumin synthesis	• Protein-calorie malnutrition • Systemic inflammation • Illness • Liver failure • Increase muscle catabolism	HD
Increased albumin utilization	• Increased fractional catabolic rate	
Exogenous albumin loss	• Urinary loss, for example, proteinuria • Residual kidney function (prealbumin was renally cleared) • Dialysis loss, especially in PD patients with peritonitis	CKD HD, PD

HD, Hemodialysis; *PD*, peritoneal dialysis.

discern between true malnutrition versus inflammation-induced reduction in serum albumin [23].

Another limitation to using prealbumin is that it is cleared by the kidneys [5] and its level may vary by estimated glomerular filtration rate [1].

Normalized protein catabolic rate or normalized protein nitrogen appearance

nPCR, otherwise known as normalized protein nitrogen appearance (nPNA), is used to estimate daily protein intake. In HD patients, nPCR is calculated by comparing pre- and post-HD blood urea nitrogen (BUN) [24,25]. In PD, nPCR is calculated by using urea of the PD fluid and BUN [25].

While serum BUN measurements may provide accurate estimates of nPCR among dialysis patients, the calculations typically underestimate nPCR in patients with a significant amount of residual kidney function (RKF) [26,27]. In patients with RKF or in CKD patients, a 24-hour urine urea collection is typically required to calculate a more accurate nPCR.

Among dialysis patients, research has shown that nPCR is correlated with serum albumin [12] and prealbumin [22]. Additionally, lower levels of nPCR have been associated with a higher risk of mortality, but point estimates for this association are lower than compared to the point estimates for the association between serum albumin and mortality [28].

Serum cholesterol

Lipid derangements are common among CKD patients and while higher cholesterol levels are typically reflective of a good nutrition status, there are many factors (not the least being the ubiquitous use of statins among this high-risk group) that drive cholesterol levels that have made this the least reliable method for determining nutritional adequacy among CKD patients. In the absence of other factors, CKD patients generally have higher plasma triglyceride and very-low-density lipoprotein (LDL) cholesterol levels along with lower high-density lipoprotein levels [29,30]. Total-density lipoprotein and LDL cholesterol are generally normal or may decrease [31]. Among patients with nephrotic syndrome, high cholesterol and LDL levels are common [32]. In addition to cholesterol-lowering medication, other conditions such as urinary or gastrointestinal protein losses along with liver disease can affect serum cholesterol levels further limiting its generalizability as a marker of malnutrition [1].

Body mass

The human body comprises both solid mass (musculoskeletal or fat) and liquid mass (intravascular or interstitial fluid). In defining PEW, researchers have separated out two distinct criteria associated with body mass: decreased total body mass and low muscle mass. In clinical practice, weight and body mass index (BMI) are readily available markers of total body mass, but these have their own limitations as we will discuss. Additionally, muscle mass can be more difficult to measure quickly in a clinical setting and we will discuss some potential limitations to this definition in the next section.

Body mass index

BMI is one of the most commonly used biomarkers for body mass and normalizes weight for height [33–35]. While non-CKD patients generally have lower risks of poor outcomes among patients with a normal BMI, CKD and dialysis patients have been noted to have an “obesity paradox,” whereby overweight or obese patients who are metabolically healthy tend to have a lower risk of mortality compared to their normal-weight counterparts [36,37]. Interestingly, overweight and obese patients who are not metabolically healthy do not appear to have this lower risk of mortality [37–39].

The complex interplay between the various mass compartments (solid vs liquid) is nicely demonstrated by a study that found that obese dialysis patients with lower muscle mass (sarcopenia) had a higher risk of death compared to patients who had normal muscle mass [40]. This interplay is not readily ascertained just by looking at BMI alone. Researchers have begun to appreciate that body composition is a more important prognostic marker than assessment of BMI alone. Furthermore, nuances of body composition that have been associated with PEW and malnutrition are not completely captured by a holistic BMI approach, especially the ratio of fat, muscle, and visceral adiposity [5].

In addition to the limitations addressed previously when looking at BMI, colleagues around the world should also be mindful of population-specific BMI cutoffs to determine PEW, as these may vary by ethnicity. While BMI $<23\ \mathrm{kg/m^2}$ meets one of the criteria for PEW, Asian ethnicities typically have a lower population-averaged BMI and lower BMI values under $23\ \mathrm{kg/m^2}$ may not necessarily be reflective of PEW [41,42].

Due to the limitations of using BMI as a marker of PEW and malnutrition, the 2020 KDOQI clinical practice guideline for nutrition in CKD recommends measuring BMI periodically, but not using BMI and waist circumference (WC) for nutrition screening in polycystic kidney disease (PKD) patients [5].

Nevertheless, dynamic changes in BMI can be indicative as a risk factor for PEW, especially unintentional weight loss of greater than 5% or 10% over 3 or 6 months, respectively, may be a sign of PEW [1,5].

To monitor overall nutrition status, combined measurements of BMI and body composition are recommended at the first and subsequent visits at least every 6 months in mild–moderate CKD with increasing frequency in severe CKD given the risk of decline is typically much faster among patients with the latter stages of CKD [5].

With respect to individual components of the body, researchers have shown a significant association with greater mortality among patients with a total body fat (TBF) percentage less than 10 in nonmuscular individuals [43–45]. In addition, muscle mass loss is also a marker of PEW [46,47]. As such, assessing only the total solid component of body composition may not highlight these important differences and it is the ratio of fat, muscle, and liquid component that may be a more helpful prognostic marker of poor outcomes among CKD patients.

Lastly, there are several definitions of optimal weight among CKD patients, all of which have their strengths and weaknesses. The ideal body weight (IBW) as measured by the Hamwi method is the weight associated with the lowest mortality given patients demographic but has not been validated among CKD patients [48].

Standard body weight is derived from the Second National Health and Nutrition Examination Survey II using the median body weight of average Americans from 1976 to 1980 for height, age, sex, and frame size. Unlike the IBW, standard body weight provides just individual weight and its associations with morbidity and mortality have not been studied [25]. Additionally, the body composition of Americans has changed over the last 40 years and this definition may no longer be suitable to the modern US population, nor can it be generalizable to populations outside the United States.

Adjusted body weight is another possible definition of IBW but it is also not validated among CKD patients. This construct assumes that 25% of the excess body weight (adipose tissue) in obese patients is metabolically active tissue, which may not necessarily be true among CKD patients [49].

Among ESKD patients, desirable body weight and edema-free body weight have been used as potential ideals of "dry weight." Desirable body weight is postdialysis weight based on BMI. The lower 50th percentile of patients for desirable body weight has been associated with a higher risk of mortality among dialysis patients [34]. Similarly, edema-free body weight is an estimated dry weight [50], which is the lowest postdialysis weight after a gradual and persistent lowering of a patient's postdialysis target weight until one has achieved a weight with minimal signs or symptoms of hypo- or hypervolemia [51].

Unfortunately, this is not yet a validated and standard optimal body weight measurement among CKD patients and further research is needed to come up with a weight target that is reasonable, is easy to calculate, and is associated with a lower risk of CKD progression and mortality. In addition, we advocate for enhancing the use of body composition measurements to improve our prognostic information as well as our understanding of the complex interplay of the various body components.

Total body fat percentage

While DXA is the gold-standard method of assessing TBF percentage, there are various other potentially easier field methods that have been studied and used as a surrogate marker. TBF percentage of less than 10% is one of the criteria for the diagnosis of PEW [1].

Skinfold thickness (SKF) is one of the established methods to assess body fat (BF) among HD patients that is both simple and inexpensive [5,52]. SKF can be measured from different body sites, including biceps, triceps, pectoral, subscapular, mid axilla, abdomen, suprailiac, and quadriceps. SKF can be converted to BF percentage by several formulae based on age and gender [53−55]. In a study assessing parameters associated with malnutrition, a lower biceps skinfold as measured by skinfold calipers was associated with a worse malnutrition score among ESKD patients [56].

Additionally, triceps skinfold (TSF), NIR, and BIA have yielded consistent estimates of TBF percentage among HD patients compared with other index tests [57,58]. The BIA devices used to measure these parameters are easier to use, more portable, and potentially can be utilized effectively within a clinical setting. However, in other studies using the Segal [59] and Lukaski methods for estimating BF [60], the BIA equations overestimated TBF percentage [58] and there appears to be gender-specific variability in the assessment of BF [52]. Because of these discrepancies, SKF may be a better a preferred method for BF assessment among HD patients [61]. Among CKD patients, SKF appears to have good agreement with DXA results so utilization of SKF may be an appropriate surrogate to measure BF among mild-to-advanced CKD patients [62].

While SKF is relatively quick and easy to obtain clinically, it has its limitations. Morbidly obese patients that cannot accommodate skinfold calipers along with patients with very low fat percentage may provide inaccurate measurements [5].

While obtaining a single measurement of BF may be helpful in point prognostication, longitudinal measurements likely have higher accuracy over time and changes can be used to track interventions aimed at lowering BF and increase muscle mass over [5].

In addition to SKF, regional adiposity measurements can also be indicative of nutritional status. WC is measured over the unclothed abdomen, just above the iliac crest, and is an indirect measurement of body composition. Alternatively, WC can be measured at the level of the umbilicus. It indicates abdominal fat deposition or abdominal obesity and can reflect the increased cardiovascular risk associated with excessive visceral fat [63,64]. In addition to WC, hip circumference measured at the widest diameter around the buttocks and the waist-to-hip ratio (WHR) has also been associated with cardiovascular outcomes [65]. Among PD patients, WC remains a reliable marker of abdominal adiposity despite several other factors contributing to WC, including abdominal distension from PD fluid, the presence of the PD catheter, and the presence of abdominal hernias [66].

Interestingly, WC predicts the risk of poor outcomes better in normal and overweight compared to obese patients, particularly whose BMI ≥ 35 kg/m^2. Regardless, there remains a strong correlation between WC, WHR, and cardiovascular risk among CKD patients [67] and mortality in maintenance HD (MHD) patients [68].

Muscle mass

Muscle wasting is one of the most important in the diagnosis of PEW. Decreased muscle mass of 5% or 10% over 3 or 6 months, respectively, meet one of PEW's diagnostic criteria. However, it is difficult to directly measure muscle mass loss [69], and there is a lack of clinical tools for accurately assessing accelerated muscle protein catabolism [70]. Therefore several biomarkers have been proposed as surrogate markers to assessing muscle mass loss in clinical practice.

Serum creatinine

Serum creatinine has long been utilized for indirectly assessing muscle mass, although it lacks accuracy and reproducibility [1] and can be affected by several factors, especially kidney disease, limiting its use in the majority of clinical settings (Table 12.4) [71]. A more accurate measurement of muscle mass has been derived

TABLE 12.4 Common factors affecting serum creatinine [71].

Factors affecting serum creatinine	Common conditions	Mechanism
Increased serum creatinine		
Laboratory interference	• Ketosis	• Ketones react in the picric acid assay for creatinine
	• Some cephalosporins • Flucytosine	• React in the picric acid assay for creatinine • React in the iminohydrolase assays for creatinine
Affected renal tubular function	• Cimetidine • Trimethoprim	• Inhibit renal tubular creatinine secretion
Diet	• Meat from striated muscle, especially if cooked	• Increased creatine ingestion from meat leads to increased creatinine production
Skeletal muscle	• Greater muscle mass or muscle hypertrophy	• Increase muscle creatinine generation
Ingestion of creatine supplements	• Due to the not uncommon attempt to increase physical exercise capacity	• Increased creatinine production from creatine
Decreased serum creatinine		
Diet	• Restriction of dietary protein	• Decreased creatinine generation
Skeletal muscle	• Low muscle mass or muscle loss	• Decrease in muscle creatinine generation
Physical activity	• Vigorous prolonged exercise	• May increase muscle creatinine generation

from creatinine kinetics, which assesses the total excretion of creatinine in the urine per day assuming that creatinine production is proportional to the amount of muscle mass that remains constant. Creatinine kinetics has been correlated with muscle mass measured by other methods such as CT scan or anthropometric measurements [72] and has been recommended by the 2020 KDOQI guidelines as a method to estimate muscle mass among CKD patients [5].

Obtaining creatinine kinetics requires a 24-hour urine collection, but again this measurement is also affected by other issues, including protein intake [62,71]. Among dialysis patients, urine collections may not be feasible especially among those who are oliguric or anuric. Assessing creatinine kinetics through predialysis serum creatinine levels, interdialytic changes in serum creatinine, and weekly creatinine clearance has provided similar markers of muscle mass that have been associated with mortality [28,72,73]. Similar to MHD patients, creatinine kinetics and serum creatinine have been associated with body composition, muscle mass, and mortality among PD patients [74–76].

In addition to creatinine, creatine kinase levels can be utilized as another surrogate marker of muscle mass with moderate reproducibility. It has been correlated with BF ($r = 0.47$) and fat-free mass (FFM) ($r = 0.57$) from DXA [62].

Midarm muscle circumference

MAMC is a marker of lean muscle mass. Among dialysis patients, midarm circumference (MAC) and MAMC are associated with nutritional markers, including serum albumin [77] and the 7-point Subjective Global Assessment (SGA) score, a standard method for diagnosing malnutrition [78]. MAMC is calculated from the following formula: $\text{MAMC} = \text{MAC} - (3.14 \times \text{TSF thickness})$. Decreased MAMC area >10% with the 50th percentile of the reference population meets one of the criteria for PEW [1].

Bioelectrical impedance analysis

BIA is a common technique used to estimate total body water, and from total weight, one is typically able to calculate fat and muscle mass [79]. Different types of BIA can be used to assess different components of body composition such as hydration status [80], muscle mass [81], and percent BF [82]. Body composition as measured by BIA has been associated with other nutritional measures [83,84], mortality [85], and has also been shown to be associated with mortality [43] in MHD patients.

Compared to DXA, fat mass (FM) ascertained through BIA tended to overestimate FM while underestimating FFM in MHD patients [86]. However, BIA appears to be a robust tool for measuring and monitoring TBF and lean body mass in HD patients compared with DXA. In the same study, researchers found that there was interestingly less correlation between DXA and BIA when assessing bone mineral content suggesting that BIA is likely a tool for assessing soft tissue [87].

Studies have also looked at BIA as a tool for predicting total body protein, specifically calculation of a body protein index (BPI) score that normalizes protein mass for patient height. While correlation levels were high among male HD patients, the score was less accurate among female participants limiting the generalizability of the score to a wider population. Additionally, the BPI score calculated through BIA was less accurate among PD patients [88].

While the BIA is a powerful surrogate for muscle mass, it appears to be less useful among PD patients. It is possible that fluid shifts among PD patients limit its use in this population and studies have shown a variation in agreement between BIA and DXA for assessing fat and FFM [89].

Given the effect of hydration status on assessing body composition with BIA, it has been suggested that testing should be done at least 30 minutes after the end of dialysis on a nonconducting surface to allow for redistribution of body fluids. Unfortunately, there continues to be a lack of evidence to support BIA use among CKD and PD patients.

Computed tomography scan

The abovementioned methods of assessing muscle mass can provide a surrogate marker of the muscle quantity. However, hydration status can interfere with these anthropometric and DXA measurements limiting their use, particularly among CKD and ESKD patients where volume overload is a frequent issue. While researchers have assumed a uniform hydration of 73% of lean body mass, this assumption can both overestimate or underestimate lean body mass quantification depending upon hydration status [90,91].

As surrogate measures have their limitations, CT scanning of muscle mass has become the gold standard for the detection of muscle wasting in clinical trials due to its high precision, accuracy, and reliability without interference from hydration status [92,93]. Even among oncologic patients where muscle wasting is also frequent, CT measurements of muscle mass appear to correlate highly with fat-free and appendicular skeletal muscle (SKM) mass [94]. In addition to muscle quantity, a CT scan can also assess muscle quality by its ability to detect the fatty infiltration in the muscle, which is not available by DXA [95]. Both CT and MRI have been shown to have good correlation when assessing total body SKM volume with the former being faster and typically less expensive [96].

There are various methods of CT measurements, including single abdominal CT imaging at the third lumbar vertebra level as well as complete CT imaging that utilizes a higher radiation dose. However, studies have shown that while prediction equations to calculate whole-body FFM, whole-body FM, and appendicular skeletal mass using CT scanning correlate well with DXA scanning measurements, single abdominal CT imaging does not provide as accurate a measurement and is likely not a sufficient surrogate for DXA when assessing body composition [97].

In stages 3–5 CKD patients, muscle mass evaluated by a CT scan showed the highest correlation with the MAMC followed by the Baumgartner predictive equation of SKM mass in both men and women [95].

While CT scans have yielded significant power to be able to measure muscle mass, researchers have yet to establish definitions for muscle depletion based upon these readings; hence, further studies are required to validate the clinical utility of the CT scan for assessing SKM mass in the CKD population [95].

Dietary intake

Both under- and overnutrition affect a patient's health status with low protein and/or energy intake potentially heralding PEW. Determining reliable methods to assess protein and energy intake has been challenging. Current reference standards for assessing dietary intake have food records or food diaries [5]. However, the addition of laboratory data not subject to recall bias, such as a 24-hour urine collection for urinary urea nitrogen, may improve the accuracy of dietary intake assessment.

Dietary protein intake

Patients' symptoms are currently one of the most important parts to improving patient-centered care in the CKD and ESKD (end-stage kidney disease) population [98,99]. Anorexia leading to unintentional low dietary protein intake (DPI) is evidence of PEW and predicts poor outcomes [100,101]. When assessing DPI, recommendations for ESKD patients requiring a higher daily protein intake are opposite to CKD patients who are recommended to be on a low-protein diet [5]. Reconciling these differences in the definition of PEW is challenging, but researchers have suggested that *unintentional* or involuntary low DPI of less than 0.6 g/kg/d for stages 2–5 CKD patients is one criterion for PEW [1].

DPI can be assessed by dietary records/diaries, interviews, food frequency questionnaires, or by the nPCR as determined by urea kinetic measurements [1,5].

Although food records/diaries are usually reliable and correlated with reference standards, its accuracy is mostly limited by recall bias. Training and instruction on how to do an adequate food recall, as well as at least 7 days of food records, has been shown to improve the accuracy of food records [102–104].

In addition to food records/diaries, a 24-hour urine collection for urinary urea nitrogen to assess protein intake is an underutilized but reliable method for assessing daily protein intake. Unfortunately, use is limited by patient convenience and ability to correctly collect the urine specimen. Done properly though, calculating the nPCR from a 24-hour urine collection is highly correlated with the DPI when using dietary recall as a reference standard among CKD patients [105–107]. However, overestimation can occur if protein intake is less than 1 g/kg/d or underestimation can occur if protein intake is greater than 1 g/kg/d when using the nPCR method [106].

Among PD patients, PNA normalized to desired body weight correlated well with BUN levels as a marker of DPI [107].

Dietary energy intake

Compared to DPI, dietary energy intake (DEI) encompasses a wider range of foods that contribute to a patient's energy intake, including fats and carbohydrates. When assessing for PEW, researchers have found that unintentional low DEI of 25 kcal/kg/d for at least 2 months in CKD and ESKD patients has been associated with PEW [1]. Similar to DPI, DEI can be assessed by food records/diaries and interviews [1].

While assessing energy intake through food records is usually reasonable, this method is also limited by recall bias and also tends to underestimate the energy intake [108]. In addition, among CKD and PD patients, energy intake recall methods tend to underestimate energy intake when compared to values obtained from resting energy expenditure (REE) using indirect calorimetry with the underestimation being most apparent among overweight patients [109,110].

Among HD patients, food frequency questionnaires by using the Block Brief 2000 food frequency questionnaire tended to underestimate energy intake compared to a 3-day food diary record, but simple calibration equations could be used to correct for systematic biases [111].

Comprehensive nutritional assessment

As there are several tools to diagnose and screen for PEW all having their own limitations, we recommend using a combination of various tools as a composite of nutritional indices to provide a comprehensive nutritional assessment. These assessments should be helpful in guiding clinicians to not only identify the risk factors and diagnose PEW earlier, but also allowing for earlier initiation of interventions and monitoring of clinical outcomes.

A comprehensive nutritional assessment involves medical and psychosocial histories, clinical symptoms and signs, a dietary intake assessment, anthropometric measurements, and measurement of biomarkers [5].

Composite nutritional indices

Screening for protein-energy wasting

Many tools can be utilized to diagnose PEW; however, early detection by screening CKD patients, particularly who are at risk for PEW (Fig. 12.3), can provide opportunities to initiate a *chain of nutrition care* to mitigate the outcomes of malnutrition and wasting or severe PEW in sarcopenic elderly CKD patients (Fig. 12.4).

The 2020 KDOQI guideline on nutrition in CKD suggests performing routine nutrition screening in stages 3–5 CKD patients twice a year to identify patients who have an increased risk of PEW. There is no single tool that can identify at-risk CKD patients [5] and several tools should likely be incorporated to determine signs of PEW. In addition, a multidisciplinary team, including registered dietitians, is critical to preventing, treating, and mitigating the outcomes of PEW.

Several screening tools comprising composite nutritional indices are shown in Table 12.5 [5].

Assessment tools for PEW

Subjective Global Assessment of nutrition The SGA of nutrition assesses nutritional status based upon features of the clinical history and physical examination (weight changes, eating habits, gastrointestinal symptoms, functional activity, and comorbid conditions) and was initially validated among patients undergoing gastrointestinal surgery in 1987. The SGA has been validated among ESKD patients. Among dialysis patients, a modified SGA score was associated with extracellular weight-to-body weight ratio using bioimpedance spectroscopy measurements [112]. Interestingly, one study did not show any correlation between SGA scores and dietary protein and energy intake in either CKD or ESKD patients [113].

Additionally, a higher SGA score was also associated with mortality among both HD and PD patients [28,76,114–116]. The SGA has widely been accepted as a reasonable tool for assessing nutritional status among HD patients but has not yet been accepted as diagnostic criteria for PEW among CKD patients [117,118].

Malnutrition–inflammation score The malnutrition–inflammation score (MIS), also known as the Kalantar Score, is a 30-point score assessing components of nutritional and inflammation among HD patients. MIS was found to have good agreement with SGA (subjective global assessment) [119] and strongly correlated with modified quantitative SGA score [120] in MHD patients. The MIS has also been associated with increased mortality [21,28,114,119], cardiovascular events [28], and hospitalizations [21] among HD patients.

Although the composite nutritional indices can identify poor nutritional states such as malnutrition and predict clinical outcomes in CKD and ESKD patients, their utility to detect PEW remains uncertain [5].

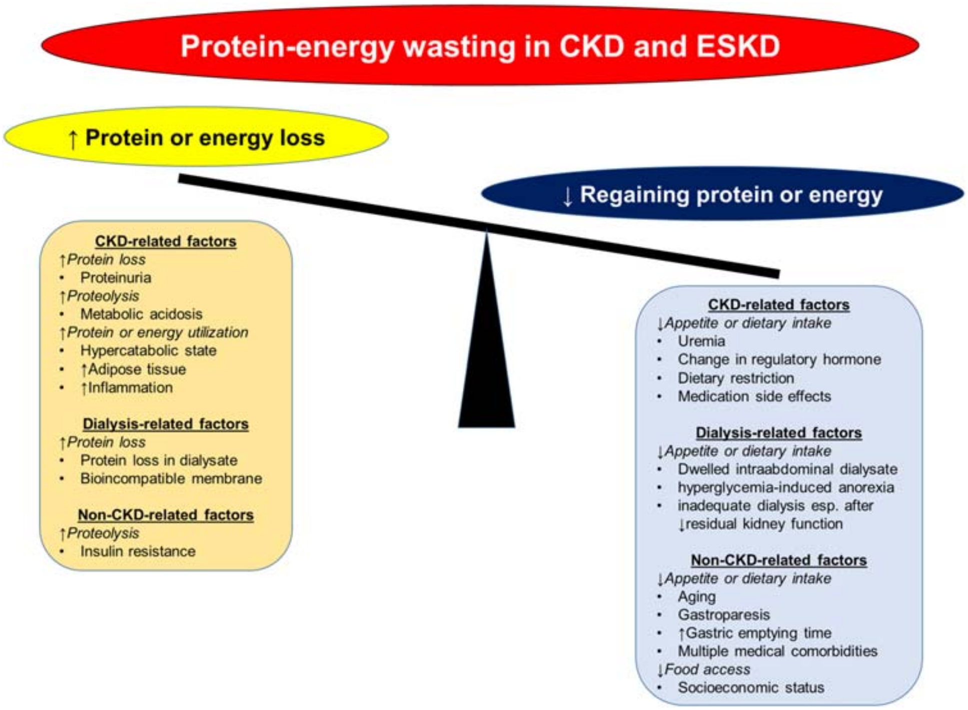
Protein-energy wasting in CKD and ESKD
↑ Protein or energy loss
↓ Regaining protein or energy
CKD-related factors
↑Protein loss
• Proteinuria
↑Proteolysis
• Metabolic acidosis
↑Protein or energy utilization
• Hypercatabolic state
• ↑Adipose tissue
• ↑Inflammation
Dialysis-related factors
↑Protein loss
• Protein loss in dialysate
• Bioincompatible membrane
Non-CKD-related factors
↑Proteolysis
• Insulin resistance
CKD-related factors
↓Appetite or dietary intake
• Uremia
• Change in regulatory hormone
• Dietary restriction
• Medication side effects
Dialysis-related factors
↓Appetite or dietary intake
• Dwelled intraabdominal dialysate
• hyperglycemia-induced anorexia
• inadequate dialysis esp. after ↓residual kidney function
Non-CKD-related factors
↓Appetite or dietary intake
• Aging
• Gastroparesis
• ↑Gastric emptying time
• Multiple medical comorbidities
↓Food access
• Socioeconomic status

FIGURE 12.3 Risk factors of protein-energy wasting in CKD and ESKD patients. *CKD*, Chronic kidney disease; *ESKD*, end-stage kidney disease.

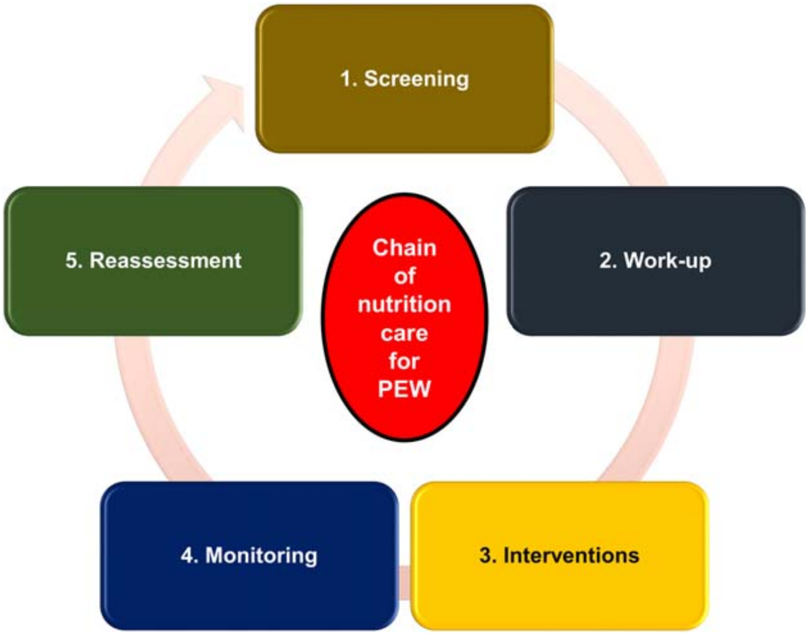
1. Screening
2. Work-up
3. Interventions
4. Monitoring
5. Reassessment
Chain of nutrition care for PEW

FIGURE 12.4 A chain of nutrition care for PEW. *PEW*, Protein-energy wasting.

Assessment for frailty

Frailty is a clinical state marked by a loss of resilience and diminished capacity to respond to health stressors and has been widely recognized as one of the important geriatric syndromes leading to poor clinical outcomes, including increased risks of falls [2,121], worsening kidney function [122], mortality, and hospitalizations [123–128]. In addition, frailty has been associated with higher cost of care compared to nonfrail

TABLE 12.5 Screening tools composing composite nutritional indices [5].

Examples of renal nutritional screening tools
• SGA
• MIS (Kalantar Score)
• Geriatric Nutritional Risk Index
• Malnutrition Universal Screening Tool/Malnutrition Screening Tool
• Mini Nutrition Assessment
• Nutrition Impact Symptoms
• Nutrition Screening Tool
• Renal Nutrition Screening Tool
• Protein-energy wasting score
• Nutrition Risk Score
• Protein Nutrition Index
• Composite Score of Protein Energy Nutrition Status
• Other measures

MIS, Malnutrition–inflammation score; *SGA*, Subjective Global Assessment.

individuals, primarily due to higher inpatient costs and higher costs near the end of life.

The prevalence of frailty is the community-dwelling older adult population is approximately 11% [129]. In the kidney disease population this prevalence is even higher with studies suggesting between 30% and 73% of ESKD patients being frail [123,124].

While there exist several tools for screening, diagnosing, and determining the severity of frailty, researchers have yet to agree on a standardized definition, likely due to the multifaceted nature of frailty [130]. Operationalizing frailty has been largely divided into three different methods: (1) the Frailty Phenotype (FP), a physical construct of frailty, (2) the Frailty Index (FI), a deficit model of frailty, and (3) the Frailty Score, a subjective construct of frailty. Each definition has its own advantages and disadvantages, but all have been linked to poor outcomes among those defined as frail.

Recent studies have shown reversibility of frailty, even among dialysis patients who are traditionally thought of as having a high degree of comorbid conditions. This reversibility suggests that prompt identification of frailty in CKD and ESKD patients may mitigate some of the poor outcomes associated with frailty.

Diagnosis of frailty

The FP is the most used frailty definition among researchers studying CKD and ESKD populations, but notably, other definitions are also associated with poor outcomes. Because the FP is defined by physical characteristics, including grip strength and gait speed, assessment of this phenotype in clinical practice is limited by availability of staff to perform this comprehensive assessment. On the other hand, the FI and Frailty Score may be easily obtained through chart review, EMR (electronic medical record) analysis, or even a cursory assessment as part of normal clinical practice.

Despite significant advances in the assessment of frailty among dialysis patients and our understanding that frailty makes patients vulnerable to poor outcomes, researchers still lack consensus on a single, easily adapted operational definition of frailty that would allow improved quantification and adequate comparison between studies. Perhaps widespread adoption of frailty assessment may not occur until a simpler construct is achieved. Alternatively, expansion of electronic health records and development of advanced data mining strategies might facilitate collection of frailty markers from various sources, including within dialysis and outpatient nephrology clinics [131]. Identification of these high-risk patients may allow tailored interventions, provide more accurate prognostic information, and improve provider-to-patient discussions on the risks and benefits of interventions such as dialysis.

Fried phenotype model of frailty

The physical construct of frailty was developed and validated by Fried et al. in a cohort of community-dwelling elderly in a study published in 2001 [2]. Individuals were considered frail if three of five major physical components of frailty were identified: shrinking or weight loss, weakness, poor endurance and energy, slowness, and low physical activity level (Table 12.6). Fried's original frailty construct has been

TABLE 12.6 Fried's Frailty Phenotype [2].

Phenotype	Measurement	Criteria
1. Shrinking	• Self-report/weight measurement	• Lost 10 lb (4.5 kg) in the past year
2. Weakness	• Dynamometer for grip strength	• Weakest 20% by gender and body mass index
3. Poor endurance and energy	• Self-report: "trouble getting going"	
4. Slowness	• Walking speed by timing a 15-ft or 5-m walk	• Slowest 20% by gender and height
5. Low physical activity level	• Self-report: number of calories expended	• Lowest 20% • Males: 383 kcal/week • Females: 270 kcal/week

See also text and Table 12.10 for the Fried criteria for Frailty Phenotype.

validated in other elderly populations as well as the CKD and dialysis populations. So far, the Fried phenotype has been the most widely used frailty construct among researchers [131].

Shrinking

Shrinking is diagnosed when either unintentional weight loss in the prior year of greater than 10 lb or greater than 5% of body weight [2]. This criterion is typically a reflection of malnutrition and/or inflammatory processes ongoing with the body leading to significant weight loss. Inflammatory processes such as CKD, cancer, chronic infection, heart failure, rheumatoid arthritis, and chronic obstructive pulmonary disease can lead to PEW and a hypercatabolic state and its associated weight loss if energy intake dips below energy expenditure [132].

In addition, weight loss needs to be interpreted with caution since some conditions in CKD patients can decrease weight abruptly such as limb amputations and aggressive volume correction in hypervolemic patients, both common among patients with CKD.

Weakness

The weakness criterion is assessed by grip strength. In Fried's FP, weakness is diagnosed when grip strength is in the lowest peer quintile and is adjusted for gender and BMI. Multiple measurements are obtained from both hands with the highest value typically being recorded for frailty assessment.

Although grip strength is a simple test done using a dynamometer, this device is not widely available in clinical practice. Staff training to properly perform the test and interpret the results is required. In addition, grip strength testing is limited in those with amputations or debilitation conditions such as a history of stroke or neurological disorder preventing full hand and arm functioning.

Poor endurance and energy

The poor endurance and energy criterion reflects the psychosocial aspect of frailty. Fried and colleagues utilized two questions regarding self-reported inability to get going from the Center for Epidemiological Studies Depression scale to define this criterion [133]. A positive response to these questions has been associated with the stage of exercise reached in graded exercise testing, has been used as an indicator of maximal oxygen consumption [134], and has also been used as a predictor of cardiovascular disease [135].

Slowness

The slowness criterion was defined by measuring walking speed over 15 ft adjusted for gender and weight. Patients in the slowest quintile were considered as meeting the slowness criterion for frailty. Gait speed remains one of the easiest and fastest methods for determining functional status among both CKD and dialysis patients, including during the prekidney transplant assessment. This criterion is, however, limited among those unable to walk such as amputees, those who are wheelchair bound, patients with severe visual impairment hindering their ability to walk, or patients with neurological deficits preventing ambulation. In these cases, patients are usually deemed to have met the slowness criterion but there are several examples of spinal cord injury patients who maintain excellent functional status without meeting compete frailty criteria despite the inability to walk.

Low physical activity level

This is a self-reported number of calories expended using a modified Minnesota Leisure Time Physical Activity questionnaire. The presence of low physical activity occurs at the lowest quintile for each gender (383 kcal/week in man and 270 kcal/week in a woman). This criterion has also been associated with coronary heart disease risk factors and subclinical disease among patients 65 years and older in the Cardiovascular Health Study [136].

Cumulative deficit model of frailty or the frailty index

There are various frailty indices that have been used to define frailty. While each differs based upon the number and type of variables, all are similar in that sum up various "deficits" and the accumulation of sufficient "deficits" then defines frailty. The "deficits" include signs, symptoms, comorbid conditions, functional impairments, and laboratory deficits that are thought to be associated with frailty. Each component typically has some correlation with the standardized comprehensive geriatric assessment that is typically used to assess an elderly patient's cognitive status, mood and motivation, communication, mobility, balance, bowel function, bladder function, activities of daily living (ADL) and instrumental ADLs, nutrition, and social resources. For example, Rockwood and colleagues developed a frailty model that included 70 different variables across a range of medical conditions, psychological conditions, and functional impairments [137] (Table 12.7). In this example the accumulation of 25% of these "deficits" defines one as being frail [138].

Frailty as defined by these various frailty indices has been associated with mortality, disease progression, hospitalization, and health-care resource utilization [139]. Unlike the FP, these frailty indices include some clinical measures that can be easily obtained from electronic medical records and laboratory data and, hence, may be a viable option for clinical settings

TABLE 12.7 Cumulative deficit model of frailty or the Frailty Index with 70 clinical components used in the Canadian Study of Health and Aging [137].

- Changes in everyday activities
- Head and neck problems
- Poor muscle tone in neck
- Bradykinesia, facial
- Problems getting dressed
- Problems with bathing
- Problems carrying out personal grooming
- Urinary incontinence
- Toileting problems
- Bulk difficulties
- Rectal problems
- Gastrointestinal problems
- Problems cooking
- Sucking problems
- Problems going out alone
- Impaired mobility
- Musculoskeletal problems
- Bradykinesia of the limbs
- Poor muscle tone in limbs
- Poor limb coordination
- Poor coordination, trunk
- Poor standing posture
- Irregular gait pattern
- Falls
- Mood problems
- Feeling sad, blue, depressed
- History of depressed mood
- Tiredness all the time
- Depression (clinical impression)
- Sleep changes
- Restlessness
- Memory changes
- Short-term memory impairment
- Long-term memory impairment
- Changes in general mental functioning
- Onset of cognitive symptoms
- Clouding or delirium
- Paranoid features
- History relevant to cognitive impairment or loss
- Family history relevant to cognitive impairment or loss
- Impaired vibration
- Tremor at rest
- Postural tremor
- Intention tremor
- History of Parkinson's disease
- Family history of degenerative disease
- Seizures, partial complex
- Seizures, generalized
- Syncope or blackouts
- Headache
- Cerebrovascular problems
- History of stroke
- History of diabetes mellitus
- Arterial hypertension
- Peripheral pulses
- Cardiac problems
- Myocardial infarction
- Arrhythmia
- Congestive heart failure
- Lung problems
- Respiratory problems
- History of thyroid disease
- Thyroid problems
- Skin problems
- Malignant disease
- Breast problems
- Abdominal problems
- Presence of snout reflex
- Presence of the palmomental reflex
- Other medical history

in which physical frailty models cannot be obtained in a reasonable time.

Many frailty indices require at least 30 items of health information for its calculation, which may be challenging to obtain quickly despite a robust clinical electronic medical record. However, researchers have found that an electronic FI can potentially be generated from primary health-care electronic medical records and frailty defined in this way has also been associated mortality, hospitalization, and nursing home admission [140].

Clinical Frailty Scale

Unlike the FP and the various frailty indices, the Frailty Scale is a subjective assessment based upon clinical judgment. It originally contained seven severity levels that corresponded to seven descriptors for levels of frailty [137]. The 7-point scale was then modified to a 9-point scale with the highest point levels reserved for terminally ill patients with less than a 6-month life expectancy (Table 12.8) [141].

While the Frailty Scale can be rapidly administered, the subjective nature of this frailty construct may lead to a wide variation among providers making this the least precise method of determining frailty. However, there have been several studies to date suggesting that even frailty based upon a subjective scale can be associated with poor outcomes (Table 12.9) [137,142–144].

Table 12.10 summarizes features of validated frailty measurement, including the FP, the FI (FI of Accumulated Deficits and FI-CGS), and the Frailty Score (Clinical Frailty Scale) [2,137,138,141,145].

Screening for frailty

Screening for frailty is not yet routinely done in clinical practice. Researchers have postulated that the

TABLE 12.8 7- and 9-Point Clinical Frailty Scale from the Canadian Study of Health and Aging.

	7-point Clinical Frailty Scale [137]	9-point Clinical Frailty Scale [141]
1. Very fit	Robust, active, energetic, well-motivated and fit; these people commonly exercise regularly and are in the most fit group for their age	Robust, active, energetic, well-motivated, and fit. Commonly exercise regularly
2. Well	Without active disease, but less fit than people in category 1	Without active disease but less fit than category 1
3. Well	With treated comorbid disease—disease symptoms are well controlled compared with those in category 4	Disease symptoms are well controlled compared with those in category 4
4. Apparently vulnerable	Although not frankly dependent, these people commonly complain of being "slowed up" or have disease symptoms	Although not frankly dependent, commonly complain of being slowed up or have disease symptoms
5. Mildly frail	With limited dependence on others for IADL	Limited dependence on others for IADLs
6. Moderately frail	Help is needed with both instrumental and non-IADL	Help is needed with BADLs and IADLs
7. Severely frail	Completely dependent on others for the activities of daily living, or terminally ill	Completely dependent for all BADLs and IADLs
8. Very severely frail		Completely dependent, approaching the end of life. Could not recover from even a minor illness
9. Terminally ill		Life expectancy <6 months but not otherwise frail

BADLs, Basic activities of daily living, including feeding, bathing, dressing, toileting, ambulation; *IADLs*, instrumental activities of daily living, including banking, transportation, cooking, cleaning, medication management, shopping.

TABLE 12.9 Clinical Frailty Scale (CFS) and clinical outcomes in different population.

	Population	Clinical outcomes associated with the CFS scores
Rockwood et al. [137]	• General	• An increased risk of death [HR 1.30 (95% CI 1.27–1.33)] and institutionalization [HR 1.46 (95% CI 1.39–1.53)]
Alfaadhel et al. [142]	• At dialysis initiation	• Mortality
Baggett et al. [143]	• Predialysis	• Mortality
Iyasere et al. [144]	• Older patients on assisted peritoneal dialysis and hemodialysis	• Worse health-related quality-of-life scores

CI, Confidence interval; *HR*, hazard ratio.

reason for this lack of assessment is multifactorial. First, clinicians typically have only a cursory understanding of frailty and its components. Second, there is no current standardized method for assessing frailty. Third, assessment of the FP requires specialized equipment and time, neither of which are found in abundance in a typical CKD or primary care clinic. Last, most electronic medical records lack the capability of a sufficiently thorough automatic chart review to make a rapid determination of frailty based upon a FI.

However, given the advances in our understanding of frailty as well its associations with poor outcomes, regardless of the method by which it is defined, many researchers are seeing the benefits of obtaining an additional prognostic factor when discussing treatment goals, especially treatments that require an ongoing lifelong commitment such as dialysis. Keeping in mind that frailty can also potentially be reversed, there are calls for early initial and subsequent screenings for frailty. Early identification can lead to early intervention while a worsening in frailty score can herald poor outcomes and provide an objective measure from which to discuss possible transitions of care (e.g., decremental dialysis regimens and/or hospice).

Treatment of frailty

While there are currently no established treatments for frailty, much research has gone into potentially increasing strength training and exercise capacity to reduce or improve frailty. In addition, studies assessing depression screening and improvement in depression scores have been potentially associated with improvements in frailty. Studies shown such breadth of interventions can potentially change a patient's frailty status show how frailty is not only defined by a physical measurement and muscle mass but also encompasses a psychosocial component. Future research into the pathophysiological basis of frailty may lead to new avenues through which we can potentially decrease the incidence and prevalence of frailty and ultimately mitigate poor outcomes among our patients.

TABLE 12.10 Features of validated frailty measurement, including Frailty Phenotype, Frailty Index of Accumulated Deficits (FI-CD), FI of Comprehensive Geriatric Assessment, and Clinical Frailty Scale (CFS) [2,137,138,141,145].

FI/origin	Components	Diagnostic criteria	Pros	Cons
Fried's Frailty Phenotype/CHS in the United States	• 5 items (shrink, weakness, poor endurance and energy, slowness, and low physical activity level)	• Robust = none • Prefrail 1–2 items • Frailty ≥ 3 items	• Widely utilized both clinical and research settings • Foundation of biological causative theory • Predicting adverse clinical outcomes	• Some items are not routinely used in clinical, practice for example, grip strength • No CGA (comprehensive geriatric assessment) • No psychological component • Potential misclassification • No severity of frailty
FI-CD/CSHA in Canada	• 30 + • Accumulated health deficits: score of 0 (no deficits) to 1 (all deficits)	• A continuous score • Frailty cutoff suggested >0.25	• Utilized both clinical and research settings • Incorporate CGA • No required special equipment • Predicting adverse clinical outcomes	• Cumbersome and take 20–30 min to complete the assessment
FI-CGS/CSHA in Canada	• 30 + • 10 domains, 52 items (originally 14): including ADL, IADL, comorbidities, mood, and cognition	• A continuous score • Frailty cutoff suggested >0.25	• Incorporate CGA • No required special equipment • Predicting adverse clinical outcomes	• Utilized only in clinical setting
CFS/CSHA in Canada	• Visual and written chart for frailty with 9 graded pictures (originally 7 points) • 1 = very fit; 9 = terminally ill	• A continuous score • Frailty cutoff point ≥5	• No required special equipment • Predicting adverse clinical outcomes	• Utilized only in clinical setting • No incorporated CGA

ADL, Activities of daily living; *CHS*, Cardiovascular Health Study; *CSHA*, Canadian Study of Health and Aging; *IADL*, instrumental activities of daily living.

Risk factors of protein-energy wasting and frailty

Risk factors of protein-energy wasting

In CKD and ESKD, risk factors of PEW include those related and unrelated to CKD (Fig. 12.3). In general, these include conditions that lead to an increased loss of protein or energy (e.g., catabolic conditions, inflammation, and stress) and/or a decreased intake of protein or energy (i.e., inadequate nutrient intake). The factors specifically related to CKD are a chronic inflammatory milieu from CKD itself, anemia, acidosis, decreased levels of or resistance to anabolic hormones [e.g., insulin, growth hormone, and insulin-like growth factor 1 (IGF-1)], and increased levels of catabolic hormones (e.g., parathyroid hormone and glucagon) [146].

Increased loss of protein or energy

Chronic kidney disease–related factors

Increased protein loss Proteinuria, particularly in when in the nephrotic range (>3.5 g/day), increases the risk of protein loss. In addition, while most proteins are retained with HD, smaller sized proteins may be dialyzable potentially contributing to increased protein loss [146]. Interestingly, patients with nephrotic range proteinuria may improve their proteinuria levels as residual renal function continues to decline [147].

Increased proteolysis Proteolysis may develop more readily in the acidic environment typically found among CKD and ESKD patients due to a decrease in proton secretion and bicarbonate regeneration [148]. Correction of metabolic acidosis may slow progression of CKD and subsequently improve nutritional status [149], decrease protein degradation and amino acid oxidation [150], decrease whole-body protein degradation in MHD patients [151], and improve acid–base status and nutrition in CAPD (continuous ambulatory peritoneal dialysis) patients [152]. While correction of acidosis has been associated with beneficial outcomes, the role of bicarbonate supplementation on improving muscle mass in HD patients with PEW remains unclear [153].

Increased protein or energy utilization Hypercatabolic states such as those found in CKD and ESKD patients can potentially increase REE by 10%–20% and subsequently lead to PEW [154]. The hypercatabolic state is typically due to underlying inflammation and high proinflammatory cytokine levels and oxidative stressors that ultimately lead to an increased energy expenditure. Despite this increase in REE, net energy expenditure may decrease among these patients due to a more sedentary lifestyle and a decrease in physical activities leading to weight gain and sarcopenic obesity [155,156]. Among those who are obese, high levels of adipose tissue lead to an increase cytokine and CRP levels further exacerbating sarcopenic obesity [157,158].

In some patients with poor baseline energy expenditure, the hypercatabolic states in CKD and ESKD ultimately lead to malnutrition, weight loss, and PEW.

Dialysis-related factors

Increased protein loss Protein losses through dialysis are not negligible and can be as high as 4–8 g/day among both peritoneal and HD patients [159]. For PD patients, high transporters may even have a higher effluent protein loss [160–163]. In addition to the protein loss in the dialysate, a reduction in protein synthesis can also lead to lower protein levels and subsequent PEW [164,165].

Among HD patients, the use of bioincompatible membranes can cause additional amino acid losses and dialyzer reuse, especially when treated with bleach, and has been associated with up to 20 g of protein loss per dialysis treatment [159].

Non-CKD-related factors

Increased proteolysis Insulin resistance in MHD patients both with [166] and without [167] type 2 diabetes has been associated with muscle protein breakdown. Furthermore, adiposity is one contributing factor to insulin resistance [168] that may in turn lead to further muscle protein breakdown.

Decreased regaining protein or energy

Chronic kidney disease–related factors

Decreased appetite or dietary intake Advanced CKD can lead to poor dietary intake as a result of uremic toxins, inflammation, and underlying medical and psychological illnesses, including depression or dementia [146].

Many factors affect appetite, including a change in regulatory hormones (e.g., leptin [169–171] and visfatin [172]) and inflammatory cytokine levels [101]. Furthermore, imposed dietary restrictions as well as polypharmacy, especially with phosphate binders or other medications that can cause gastrointestinal-related side effects, can also cause low caloric intake [173].

Dialysis-related factors

Decreased appetite or dietary intake Among PD patients, dwelled intraabdominal dialysate can cause fullness and decreased appetite independent of the intragastric pressure increases from dialysate [174].

Moreover, hyperglycemia from glucose absorption from peritoneal dialysate either from continuous glucose absorption [175] or when using hypertonic dialysate exchanges in volume overload can suppress appetite through hyperglycemia-induced anorexia [175,176].

Additionally, the poor appetite may result from inadequate dialysis and uremic toxin buildup, especially with inappropriate or unadjusted dialysis prescriptions when residual renal function declines. On the other hand, longer dialysis duration can also predispose to greater risk of inadequate energy and protein intake [177].

Non-CKD-related factors

Decreased appetite or dietary intake Several non-CKD-related factors can also be associated with decreased appetite and dietary intake. Aging itself is also associated with decreased DPI in elderly men [178], and among diabetic CKD, patients with gastroparesis and delayed gastric emptying can exacerbate low appetite. Addition of other medical comorbidities such as congestive heart failure, chronic pulmonary diseases, and malignancies is also associated with PEW [179].

Decreased food access Poor socioeconomic status contributes to food insecurity that leads to poor nutrition and can also lead to volume overload from edematous states in ESKD [146].

Risk factors of frailty

CKD and age remain two of the strongest risk factors for frailty, though neither age nor comorbidities are enough for the diagnosis of frailty. Additional comorbidities related to CKD also play an important role (Table 12.11 and Fig. 12.5).

Aging

Age-related frailty may result from genetic or environmental factors.

Genetic factors

Muscle abnormalities (sarcopenia) We are beginning to understand that some neurohormonal pathways are related to human longevity and SKM. For example, age-related growth hormone deficiency can lead to decreased levels of IGF-1, an anabolic, antiapoptotic hormone that has been shown to maintain muscle mass and improve physical performance [180,181]. The loss of muscle mass and strength (i.e., sarcopenia) can ultimately decrease exercise capacity and potentially lead to frailty [182].

Vitamin D deficiency, common among elderly and patients with decreased skin thickness, is also associated

TABLE 12.11 Pathogenesis of frailty in chronic kidney disease and end-stage kidney disease patients.

1. Aging	
1.1 Genetic factors	
1.1.1 Hormonal pathways	
Sarcopenia	• ↓Growth factors • ↓IGF-1 • Resistance to anabolic hormones • Enhanced actions of some catabolic hormones (glucagon) • Anorexia with protein-energy malnutrition • Markedly reduced physical activity • Intercurrent catabolic illnesses
Type II (fast) muscle fiber atrophySkin thickness	• Vitamin D deficiency
1.1.2 Neuronal abnormalities	
Structural and functional neuromuscular disorders	• Loss lower motor neurons in the L1–L3 • Conversion of type II fibers to type I fibers for denervation of type II fibers • ↓Percent of type II fibers • ↓The number of satellite cell (muscle stem cell) • ↓Satellite cell proliferation and differentiation • Muscle protein synthesis • ↑Tendon compliant • ↑Fat mass rather than ↓fat-free mass
1.2 Environmental factors	
1.2.1 Gene and chromosome-related factors	
Accumulated dysfunctional senescent cells, tissues, and organ systems	• Oncogene expression • DNA damage • Telomere shortening • Dysfunction of cellular organelle, for example, mitochondrial dysfunction • Cellular apoptosis and autophagy • Inflammatory process, for example, oxidative stress, free radical accumulation
2. CKD-related factors	
2.1 Physical inactivity	
Structural and functional neuromusculoskeletal abnormalities	• Metabolic disturbances • Uremic neuropathy
Loss in type II fibers	• 25(OH)D deficiency • 1,25-(OH)2D deficiency
Tendomuscular structures	• CKD-MBD from tendon calcification
3. Non-CKD-related factors	
3.1 Physical inactivity	
Medical	• Congenital or acquired causes of neuromuscular disorders • Medical comorbidities
Psychological	• Depression • ↓Motivation to exercise or perform physical activity
Sociocultural factors	• Lack of education or awareness

1,25-(OH)2D, 1,25-Dihydroxycholecalciferol; *25(OH)D*, 25-hydroxycholecalciferol; *CKD-MBD*, chronic kidney disease-mineral bone disorder.

with type II muscle fiber atrophy and a subsequent decrease in physical performance [183–185].

Neuronal abnormalities In addition to muscular issues that can contribute to frailty, neurological issues may also contribute to sarcopenia and frailty in the elderly. These neurological issues include the loss of lower motor neurons, especially in elderly individuals over 60 years old as well as a decrease in the number and diameter of motor axons, a decrease in peroneal nerve conduction velocity, and a reduction in compound muscle action potentials [186,187].

Denervation found in elderly individuals also causes a disproportionate loss of fast muscle motor units (type II fibers) compared to the slow motor units (type I fibers). The loss of type II fibers also causes a net conversion of type II fibers to type I fibers due to the recruitment of denervated type II fibers by the surviving type I fibers [188,189].

Satellite cell proliferation and differentiation are decreased in the elderly due to decreased or delayed expression of myogenic regulatory factors, including myogenic determination factor, myogenic regulatory factor 5, and myogenin [190].

Environmental factors

Gene- and chromosome-related factors Environmental factors that contribute to frailty include abnormal gene and chromosome such as oncogene expression, DNA damage, telomere shortening [191–193], dysfunction of cellular organelles such as mitochondrial dysfunction [194,195], cellular apoptosis and autophagy [196,197], and inflammatory process such as oxidative stress [194,195], and free radical accumulation [193,198]. These lead to accumulated dysfunctional senescent cells, tissues, and organ systems [193,199] that can also lead to frailty over time.

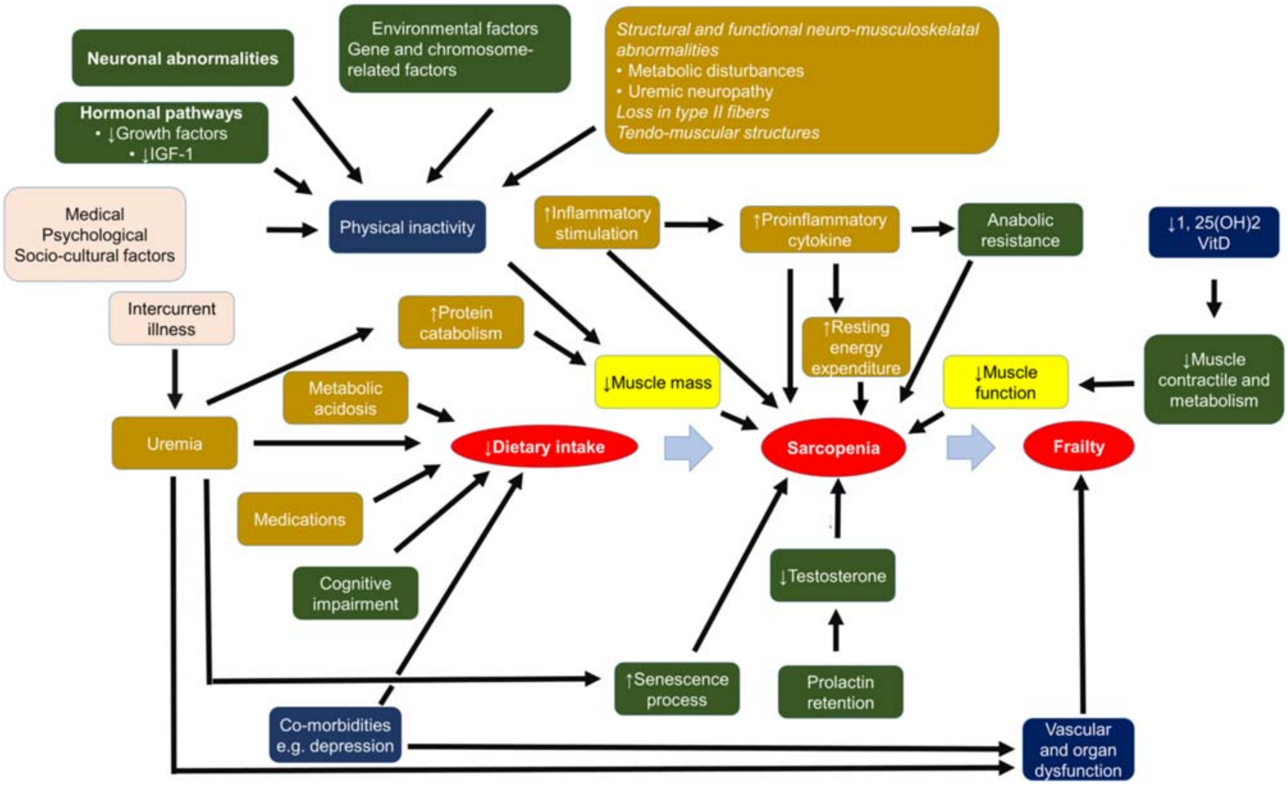
Neuronal abnormalities
Environmental factors
Gene and chromosome-related factors
Structural and functional neuro-musculoskelatal abnormalities
• Metabolic disturbances
• Uremic neuropathy
Loss in type II fibers
Tendo-muscular structures
Hormonal pathways
• ↓Growth factors
• ↓IGF-1
Medical
Psychological
Socio-cultural factors
Physical inactivity
↑Inflammatory stimulation
↑Proinflammatory cytokine
Anabolic resistance
↓1, 25(OH)2 VitD
Intercurrent illness
↑Protein catabolism
↑Resting energy expenditure
↓Muscle mass
↓Muscle function
↓Muscle contractile and metabolism
Metabolic acidosis
Uremia
↓Dietary intake
Sarcopenia
Frailty
Medications
Cognitive impairment
↓Testosterone
↑Senescence process
Prolactin retention
Co-morbidities e.g. depression
Vascular and organ dysfunction

FIGURE 12.5 Pathophysiology of frailty in CKD and end-stage kidney disease patients. Three main factors include aging (*green boxes*), CKD (*brown boxes*), non-CKD (*pink boxes*), and combined factors (*blue boxes*). *1,25-(OH)2D*, 1,25-Dihydroxycholecalciferol; *25(OH)D*, 25-hydroxycholecalciferol; *CKD*, chronic kidney disease; *IGF-1*, insulin-like growth factor 1.

Chronic kidney disease–related factors

There are also many CKD-related factors that should be considered. Metabolic disturbances from CKD can lead to both structural and functional neuromusculoskeletal abnormalities. In addition, uremia causes impaired sensation, hypoesthesias, reduced deep tendon reflexes, paresis, and paralysis [146]. These can potentially contribute to decreased ambulation and other types of physical activity, especially in a population that is already prone to physical inactivity [200].

Vitamin D deficiency due to CKD can also result in abnormalities in muscle function placing CKD and ESKD patients at greater risk of frailty and sarcopenia compared to non-CKD patients. In addition, high calcium deposition found in late CKD and ESKD patients may interfere with tendomuscular structures and function that can result in rupture or separation of tendons from their bony insertion sites when subjected to increased contractile force [201,202]. These factors ultimately can lead to low physical activity and frailty.

Non-CKD-related factors

In addition to CKD-related factors that contribute to the development of frailty, there are non-CKD-related factors such as psychological and sociocultural factors that may also increase the risk of developing frailty. For example, congenital or acquired medical conditions leading to neuromuscular disorders can prevent individuals from being active such as congenital or acquired causes of neuromuscular disorders. Also, mental disorders such as depression can decrease their motivation to exercise or perform physical activity in addition to itself being a risk factor for frailty [203]. Sociocultural issues and the lack of health literacy can also predispose to unhealthy lifestyle habits and a lower level of physical activity.

The dynamic interaction between PEW and frailty overtime through the CKD spectrum ultimately leads to additional age-related syndromes such as cachexia and sarcopenia (Fig. 12.6). Both PEW and frailty are complex clinical syndromes with overlapping pathophysiology that contribute to poor patient outcomes, especially among CKD and ESKD patients. While researchers have yet to determine a standard definition of frailty, the field is constantly evolving, and our understanding of these complex clinical syndromes is continuously improving. With advances in this field, we hope that the development of better screening tools can assist with furthering identifying at-risk patients, improving prognostication to

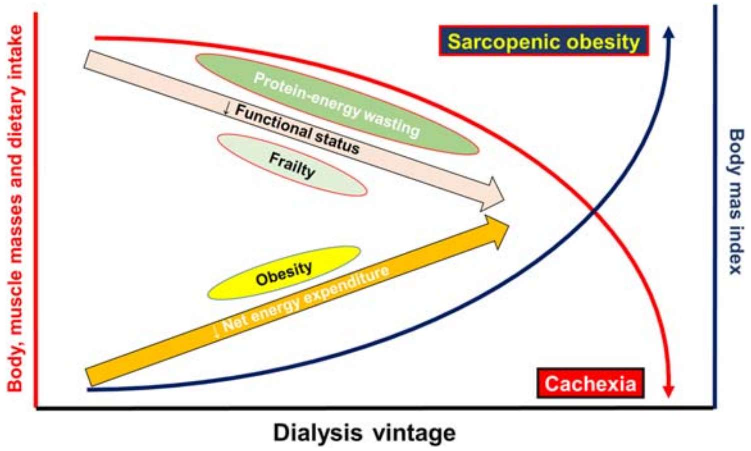

FIGURE 12.6 Dynamic of protein-energy wasting and frailty in chronic kidney disease and end-stage kidney disease patients. The longer the dialysis vintage, the higher the risk of protein-energy wasting and frailty. The severe frailty spectrum is cachexia. However, with a decrease in net energy expenditure, body mass index may increase and this leads to another phenotype of the frailty of sarcopenic obesity.

better counsel our patients, and mitigating unfavorable outcomes in this high-risk population.

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Abbreviations

ADL	activities of daily living
BADL	basic activities of daily living
BF	body fat
BIA	bioelectrical impedance analysis
BMI	body mass index
BUN	blood urea nitrogen
CFS	Clinical Frailty Scale
CHS	Cardiovascular Health Study
CI	confidence interval
CKD	chronic kidney disease
CSHA	Canadian Study of Health and Aging
CT	computed tomography
DEI	dietary energy intake
DPI	dietary protein intake
DXA	dual-energy X-ray absorptiometry
ESKD	end-stage kidney disease
FFM	fat-free mass
FI	Frailty Index
FI-CD	Frailty Index of Accumulated Deficits
FM	fat mass
GFR	glomerular filtration rate
HD	hemodialysis
HR	hazard ratio
hsCRP	high-sensitive C-reactive protein
IADL	instrumental activities of daily living
IBW	ideal body weight
L	lumbar
MAMC	midarm muscle circumference
MHD	maintenance hemodialysis
MIS	malnutrition–inflammation score
NIR	near-infrared interactance
nPCR	normalized protein catabolic rate
nPNA	normalized protein nitrogen appearance
PD	peritoneal dialysis
PEW	protein-energy wasting

REE	resting energy expenditure
SGA	Subjective Global Assessment
SKF	skinfold thickness
TBF	total body fat
TSF	triceps skinfold
WC	waist circumference
WHR	waist-to-hip ratio

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CHAPTER

13

Causes and treatment of protein-energy wasting in kidney disease

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Protein-energy wasting (PEW), defined as "loss of body protein mass and fuel reserves," is one of the most serious complications of chronic kidney disease (CKD) and is frequently encountered not only in nondialyzed patients with advanced CKD but also in those individuals with end-stage renal disease (ESRD) who are receiving maintenance hemodialysis (HD) or chronic peritoneal dialysis (PD) therapy. There are many causes of PEW in CKD, and these include a wide array of disorders or factors that may or may not be related directly to the underlying renal failure: anorexia, decreased nutrient intake, endocrine disorders, inflammatory cytokines, metabolic acidosis, oxidative and carbonyl stress, volume overload, comorbid conditions, nutrient loss during the dialysis procedure, and other dialysis treatment–related factors. Multifaceted and individualized approaches are required for the prevention and treatment of PEW, including optimizing dietary nutrient intake and physical exercise, prescribing optimized dialytic regimens, and appropriate treatment of metabolic disturbances such as hormonal deficiencies, metabolic acidosis, and systemic inflammation. A number of interrelated mechanisms and mediators involved in the pathophysiology of PEW in CKD, as well as its therapeutic maneuvers, are discussed.

Introduction

PEW represents one of the most serious complications of CKD [1] and poses a formidable therapeutic challenge because (1) it is common and is frequently encountered not only in individuals with ESRD who are receiving maintenance HD or chronic PD therapy but also in nondialyzed patients with CKD, (2) it is caused by a wide range of disorders or factors that may or may not be related directly to the underlying kidney disease [2], and (3) it can cause severe and prolonged debilitation leading to poor quality of life. In addition, PEW assumes an even greater significance because it often coexists with other comorbid risk factors, such as diabetes, inflammation, and atherosclerosis, and is powerfully associated with all-cause mortality, adding further to the excess morbidity and mortality in the ESRD population [3,4].

In recent years, it has become increasingly apparent that the wasting syndromes attributed to PEW are not merely the result of undernutrition with reduced intake of protein and energy but may also involve other factors or conditions that reduce muscle mass or increase fat loss and/or energy expenditure. Based on new findings concerning syndromes of muscle wasting, malnutrition, and inflammation in individuals with acute kidney injury (AKI), or CKD, the International Society of Renal Nutrition and Metabolism (ISRNM) expert panel proposed in a 2008 report new terminologies and definitions related to wasting, cachexia, malnutrition, and inflammation [5]. The term "protein-energy wasting," previously referred to as "protein-energy malnutrition," is now defined as the state of decreased body stores of protein and energy fuels (i.e., body protein and fat masses). "Kidney disease wasting" is used by some nephrologists to refer to the occurrence of PEW in CKD or AKI, regardless of the cause. Since many causes of PEW in CKD or AKI are similar to the causes of PEW in other chronic or acute diseases, many nephrologists prefer to use the term PEW for protein and/or energy wasting that occurs in kidney disease. This emphasizes the similarity for most causes of PEW in these various disease states. Cachexia refers to a severe form of PEW

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TABLE 13.1 Protein-energy wasting (PEW) diagnostic criteria suggested by the PEW consensus conferences [5].

Primary criteria
1. Biochemical markers **2.** Body composition indices **3.** Muscle mass **4.** Dietary intake
Supportive criteria
1. Appetite, food intake, and energy expenditure **2.** Body mass and composition **3.** Other laboratory biomarkers **4.** Nutritional scoring systems **5.** Other novel markers

that occurs infrequently in kidney disease. Diagnostic criteria for PEW are shown in Table 13.1. While markers of chronic inflammation or other novel biomarkers can be useful clues for the existence of PEW, such measures do not define the condition.

This chapter focuses on the causes and treatment of PEW in CKD and examines the evidence for the role of molecular, biochemical, nutritional, as well as environmental factors involved in the pathogenesis of PEW, which in turn is key to formulating strategies for the prevention and treatment of this common and debilitating disorder.

Causes of protein-energy wasting in chronic kidney disease

PEW may be viewed as a complex heterogeneous disorder that results from an interplay of multiple factors that directly or indirectly alter protein metabolism and energy balance. There are many causes of PEW in CKD, and these encompass a wide variety of conditions or disorders that ultimately lead to decreased protein and energy intake, increased protein loss or energy expenditure, or a combination of both factors as shown in Table 13.2.

TABLE 13.2 Causes of protein-energy wasting in chronic kidney disease/end-stage renal disease.

1. Anorexia
2. Decreased nutrient intake
3. Endocrine disorders:
    insulin resistance
    decreased insulin-like growth factor-I
    hyperglucagonemia
    testosterone deficiency
    vitamin D deficiency
    hyperparathyroidism
4. Inflammation
5. Oxidative and carbonyl stress
6. Metabolic acidosis
7. Volume overload
8. Comorbid conditions, including diabetes and cardiac failure
9. Nutrient loss during dialysis treatment
10. Increased energy utilization
11. Abnormal protein kinetics

Pathophysiology of protein-energy wasting in chronic kidney disease

The pathophysiologic basis of PEW in CKD is multifactorial as depicted in Fig. 13.1. Before discussing the mechanisms of wasting in CKD, a few general considerations merit special attention. First, the factors involved in the regulation of nutrient intake, protein metabolism, and energy balance are diverse, and their relative contribution to wasting in PEW may vary in importance depending upon the nature of the inciting stimulus or event that occurs during the evolution of the disease. Second, given the chronicity and varying comorbid conditions associated with CKD, mechanisms that initiated PEW may not be operative at the later stages of the disease, and as kidney disease progresses to end stage, other potential mechanisms may come into play. Third, there are inherent redundancies in molecular, cellular, and biochemical events that regulate protein and energy metabolism in a given individual, as there are in the biologic activities of various peptides, cytokines, and hormones. Thus there are independent, overlapping, and complementary or antagonistic mechanisms of action, which make it difficult to disentangle their effects on protein metabolism and/or energy balance. Nonetheless, the accumulated scientific data may provide the framework for formulating targeted interventions to prevent or reverse PEW in patients with CKD.

Anorexia

Anorexia is a cardinal manifestation of CKD. Several factors have been proposed to account for the anorexia associated with kidney disease. Evidence that uremic toxins can suppress appetite and food intake is derived from the studies of Anderstam and coworkers [6] in experimental animals showing that intraperitoneal injection of uremic plasma ultrafiltrate into normal rats inhibits ingestion of nutrients. A dose-dependent effect was noticed only with the subfractions with molecular weight ranges of 1–5 and 5–10 kDa, respectively, whereas fractions with molecular weights below 1 kDa had no effect. In a subsequent study the same group of investigators showed that intraperitoneal injection of a

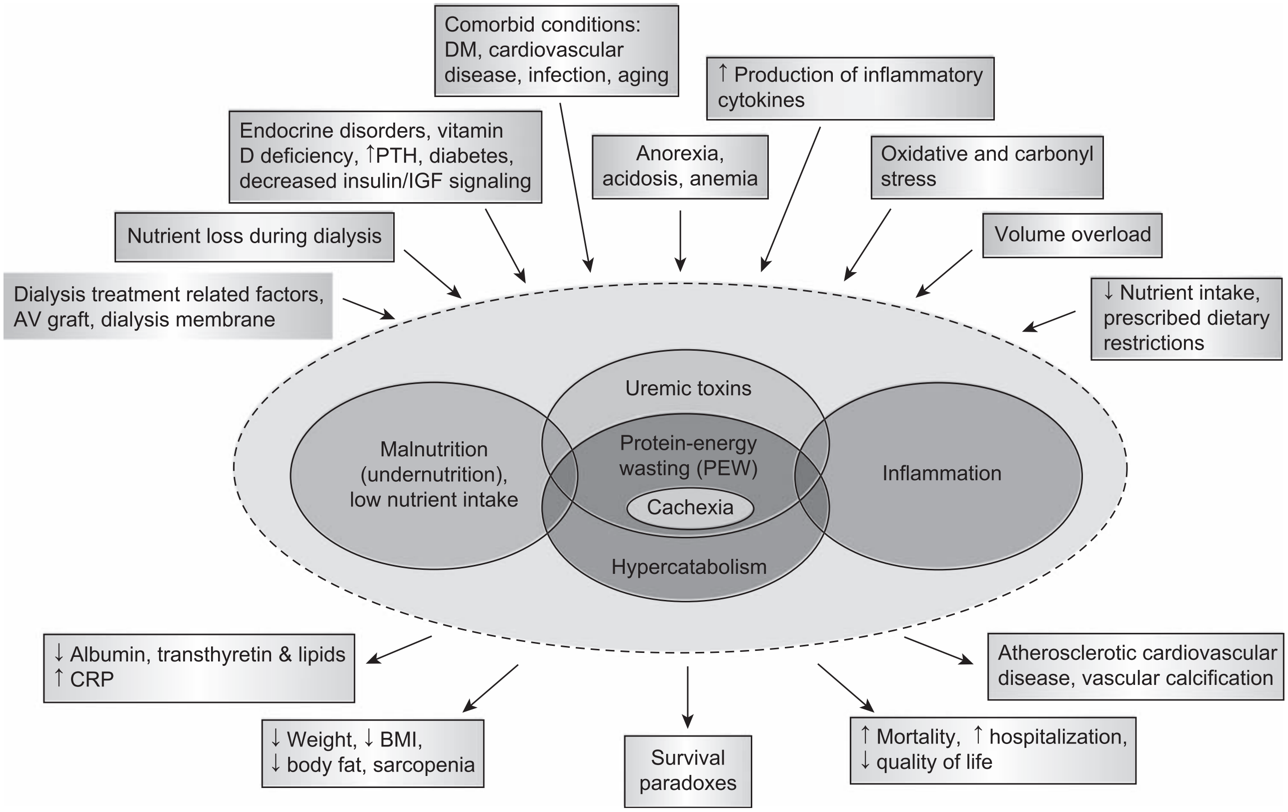
Comorbid conditions: DM, cardiovascular disease, infection, aging
↑ Production of inflammatory cytokines
Endocrine disorders, vitamin D deficiency, ↑PTH, diabetes, decreased insulin/IGF signaling
Anorexia, acidosis, anemia
Oxidative and carbonyl stress
Nutrient loss during dialysis
Volume overload
Dialysis treatment related factors, AV graft, dialysis membrane
↓ Nutrient intake, prescribed dietary restrictions
Uremic toxins
Malnutrition (undernutrition), low nutrient intake
Protein-energy wasting (PEW)
Cachexia
Inflammation
Hypercatabolism
↓ Albumin, transthyretin & lipids ↑ CRP
Atherosclerotic cardiovascular disease, vascular calcification
↓ Weight, ↓ BMI, ↓ body fat, sarcopenia
Survival paradoxes
↑ Mortality, ↑ hospitalization, ↓ quality of life

FIGURE 13.1 Schematic representation of the causes and manifestations of the protein-energy wasting syndrome in kidney disease. Source: *Reprinted from Fouque D, Kalantar-Zadeh K, Kopple J, et al. A proposed nomenclature and diagnostic criteria for protein-energy wasting in acute and chronic kidney disease. Kidney Int 2008;73:391–8.*

urine fraction or uremic plasma ultrafiltrate fraction inhibited carbohydrate intake by 76.3% and 45.9%, respectively [7]. An intracerebroventricular injection of 5 or 10 μL of urine middle molecule fraction (i.e., compounds with a molecular weight range of 300–2000 Da) significantly inhibited carbohydrate intake. These data suggest that middle molecule compounds that accumulate in the plasma of uremic patients suppress food intake.

Decreased nutrient intake

Inadequate nutrient intake is considered the most important single cause of PEW in CKD and has been well documented in both adults and children with varying degrees of kidney failure [5,8]. The decline in dietary intake occurs early in CKD and accelerates as renal failure worsens. In children with CKD, low protein or energy intake due to anorexia is the primary reason for growth failure in this group [9]. In a prospective study, Ikizler [10] showed that spontaneous dietary protein intake (calculated from 24-hour urine urea excretion) of patients with CKD significantly decreases as renal function declines. This decrease is most noticeable at creatinine clearance levels below 25 mL/min. In a large cohort of adult patients with moderate-to-advanced CKD, Kopple et al. [11] showed that dietary protein intake and nutritional status correlated directly with the GFR. Especially, patients with a GFR of 21 mL/min/1.73 m^2 or lower showed greater decline in nutritional status. Thus intake of dietary protein and calorie declines with decrease in GFR. The other factors that could contribute to decreased nutrient intake include depression, dementia, and even economic barriers [12].

Impaired gastric motility

Several studies have documented an impairment of gastric motility in ESRD patients [13,14]. In one study, more than 50% of nondiabetic ESRD patients receiving maintenance dialysis had abnormal gastric myoelectrical activity [15]. Furthermore, administration of prokinetic agents to hypoalbuminemic nondiabetic maintenance HD patients with occult gastroparesis was shown to improve gastric emptying, an effect that was accompanied by an increase in serum albumin [16]. The mechanism for the gastroparesis in ESRD patients is unclear, but it has been postulated that derangements in neuroendocrine signaling and imbalance in gut-derived hormones may play a pathogenic role.

Endocrine and hormonal disorders

CKD is characterized by a plethora of endocrine disorders resulting from either an increased or decreased level of hormones or impaired action at the target tissue level. We will review the association between endocrine/hormonal dysfunction and its role in the pathogenesis of PEW.

Gut-derived hormones

The gut produces peptides that have autocrine and paracrine as well as endocrine functions. These gut-derived peptides maintain mucosal integrity, facilitate secretion of digestive enzymes, modulate gut motility, and signal to the brain regarding the presence and absorptive status of nutrients; thus they could play an important role in the genesis of PEW.

Ghrelin is a unique hormone, principally secreted from the stomach. It acts to stimulate appetite and food intake via stimulation of the type 1a growth hormone (GH) secretagogue receptor [17]. Since ghrelin is a potent appetite enhancer, it was initially thought that reduced levels of circulating ghrelin might be a potential mechanism for the reduced appetite seen in CKD. Surprisingly, plasma ghrelin was found to be elevated in patients with ESRD [18], and circulating ghrelin levels were found to be significantly higher in uremic patients with poor appetite when compared with uremic patients with good appetite [19]. Subsequent studies have revealed that ghrelin circulates in both an acylated [acyl ghrelin (AG)] and des-acylated forms [des-acyl ghrelin (DG)] [20], and that AG has potent orexigenic activity and induces an increase in food intake, while DG exerts opposing actions to AG [21]. In patients with ESRD, the altered ghrelin metabolism associated with uremia results in an increased DG/AG ratio and resultant anorexigenic transcripts in the hypothalamus, which leads to decreased food intake and gastric emptying and promotes PEW [21]. Recent studies have also shown that exogenous administration of ghrelin increases AG levels and improves appetite and/or increases food intake in animals and humans with CKD [22,23]. Thus exogenous administration of ghrelin appears to be a promising strategy to improve food intake in malnourished ESRD patients.

Peptide YY (PYY) is another gut-derived hormone that plays an important role in the short-term regulation of appetite [24]. This peptide is released by intestinal L cells in response to meals, suppresses appetite, and acts as a "break" to oral intake by complex mechanisms, which include vagal stimulation through interaction with the receptor Y2 (Y2R) of the hypothalamic arcuate nucleus. Increased plasma levels of PYY have been reported in patients with ESRD treated with dialysis, which could contribute to the anorexia and PEW of CKD [25].

Cholecystokinin (CCK) is an intestinal hormone known to cause early satiety and suppress appetite [26]. It is released in response to eating and induces a state of satiety via peripheral and central receptors. Because circulating levels of CCK are increased in ESRD patients, it has been suggested that CCK may contribute to the premature satiety and anorexia in CKD. Experimentally, administration of CCK has been shown to induce premature satiety with shortening of the eating period and reduced nutrient intake [27].

Insulin and insulin-like growth factors

The most common and important endocrine disorder in CKD is the development of insulin resistance [28]. Insulin is a potent anabolic hormone; even a small increase in plasma insulin stimulates protein synthesis and exerts a powerful inhibitory effect on protein catabolism [29]. Resistance to the actions of insulin has been shown to be strongly associated with increased muscle breakdown in nondiabetic chronic HD patients [30].

Insulin-like growth factor-I (IGF-I), which has a 48% amino acid sequence identity with proinsulin, enhances insulin sensitivity and independently stimulates protein synthesis and suppresses protein degradation in both experimental animals and human subjects. Kopple and associates showed that mRNA levels of IGF-IEa, IGF-II, and the IGF-I receptor are decreased in the skeletal muscle of ESRD patients [31]. There is an attenuation in the IGF-I-induced stimulation of protein synthesis and inhibition of protein degradation in skeletal muscle in CKD [32]. Among the known mechanisms for IGF-I resistance in CKD are defects in the phosphorylation and activity of the intrinsic tyrosine kinase of the IGF-I receptor and plasma inhibitors of IGF-I and elevated basal cytosolic [Ca^{2+}] [30]. Bailey et al. [33] have shown that CKD causes defects in IGF-I signaling in skeletal muscle, an effect that is associated with a decrease in phosphorylation of Akt (protein kinase B) and an increase in proteolysis and muscle wasting. Another mechanism closely linked to impaired IGF-I signaling in CKD is dysfunction of skeletal muscle precursors or satellite cells, which are responsible for maintaining muscle growth and repair [34].

Interestingly, administration of thiazolidinedione (TZD) in a rodent model of insulin resistance improved insulin resistance and decreased protein degradation in muscle [35]. Furthermore, in a recent clinical study of a large cohort of incident HD patients with diabetes, non-insulin requiring type-2 diabetic subjects receiving TZDs had significantly higher body mass indices, and serum albumin levels, than those not receiving TZDs [36].

Resistance to growth hormone

GH is the major promoter of growth in children and exerts anabolic actions even in adults: protein synthesis, reduced protein degradation, increased fat mobilization, and increased gluconeogenesis, with IGF-I being the major mediator of these actions [37]. It also regulates muscle and fat metabolism, which impacts body composition and insulin sensitivity. Decreased or impaired action of GH is another endocrine disturbance associated with CKD that may retard muscle growth and promote muscle protein catabolism [38]. Insensitivity to GH is the consequence of multiple defects in the GH/IGF-I signaling. GH activation of the Janus kinase 2-signal transducer (JAK2) and activator of transcription (STAT) signal transduction pathway is depressed in advanced CKD, and this leads to reduced IGF-I expression and resistance to IGF-I [39]. Interestingly, similar biochemical abnormalities can also be observed with decreased dietary protein, and during experimental metabolic acidosis [40], suggesting that an interrelationship between these hormonal, metabolic, and nutritional factors is involved in the development of PEW in patients with CKD.

Testosterone deficiency

Hypogonadism is a frequent endocrine disorder in men undergoing dialysis, and more than 60% of men with advanced CKD have low plasma concentrations of testosterone [41]. Testosterone regulates many physiological processes, including sexual function, cognitive functions, erythropoiesis, plasma lipids, and bone mineral metabolism, and testosterone deficiency is associated with sexual disorders, worse quality of life, poor graft survival, and increased mortality risk [42]. In view of its physiological effects as an anabolic hormone, testosterone plays an important role in inducing skeletal muscle hypertrophy [42]. It facilitates muscle anabolism by, among other mechanisms, promoting nitrogen retention, stimulating fractional muscle protein synthesis, inhibiting muscle protein degradation, and augmenting the efficiency of amino acid reuse by skeletal muscle [43]. In patients with CKD, testosterone synthesis is severely diminished, mainly because of reduced prolactin clearance and uremic inhibition of luteinizing hormone signaling, which has been associated with reduced muscle strength and fat-free mass contributing to the development of PEW in CKD [44].

Altered adipokine physiology

Adipose tissue has traditionally been viewed as a passive reservoir for storage of energy. However, in recent years, it has emerged as a highly active endocrine organ that secretes a variety of bioactive peptides, known as adipokines, which mediate numerous biological and pathological processes, including energy metabolism, neuroendocrine function, sex steroid metabolism, and immune function. The underlying mechanisms whereby endocrine hormones and adipokines cause anorexia and decreased nutrient intake in CKD are complex and may involve the participation of neuroendocrine pathways that control food intake and energy homeostasis (Fig. 13.2).

Leptin, the protein product of the *ob*-gene, is secreted by adipocytes and acts as a lipostat mechanism to regulate food intake and energy expenditure via modulation of satiety signals in the hypothalamus [46]. An increase in the level of leptin decreases neuropeptide Y, reduces food intake, increases energy expenditure, induces weight loss, lowers plasma insulin, alters glucose homeostasis, and induces muscle protein breakdown. Serum leptin concentrations are elevated in CKD patients who do not have ESRD [47], as well as in patients undergoing renal replacement therapy [48] and have been shown to be inversely correlated with dietary protein intake [49]. Longitudinal studies have also shown that increased serum leptin levels are associated with weight loss in dialysis patients [50]. Moreover, experimental studies in leptin receptor-deficient mice made cachetic by nephrectomy have shown that uremia-associated cachexia is caused by leptin signaling through the hypothalamic melanocortin receptor 4 [51]. These results suggest that increased circulating leptin may be an important mediator of uremia-associated cachexia via signaling through the central melanocortin system. However, other anorexigenic and catabolic pathways besides leptin cascade may be important.

Adiponectin is another adipocyte-derived hormone that has been shown to modulate food intake and energy homeostasis [52]. In addition, adiponectin has insulin-sensitizing, antiatherogenic, and antiinflammatory properties. Data regarding the role of adiponectin in PEW in CKD are limited. Despite the high prevalence of insulin resistance in CKD, circulating levels of adiponectin are increased among patients with CKD [53–55]. Surprisingly, in ESRD patients undergoing maintenance dialysis serum, adiponectin levels were positively

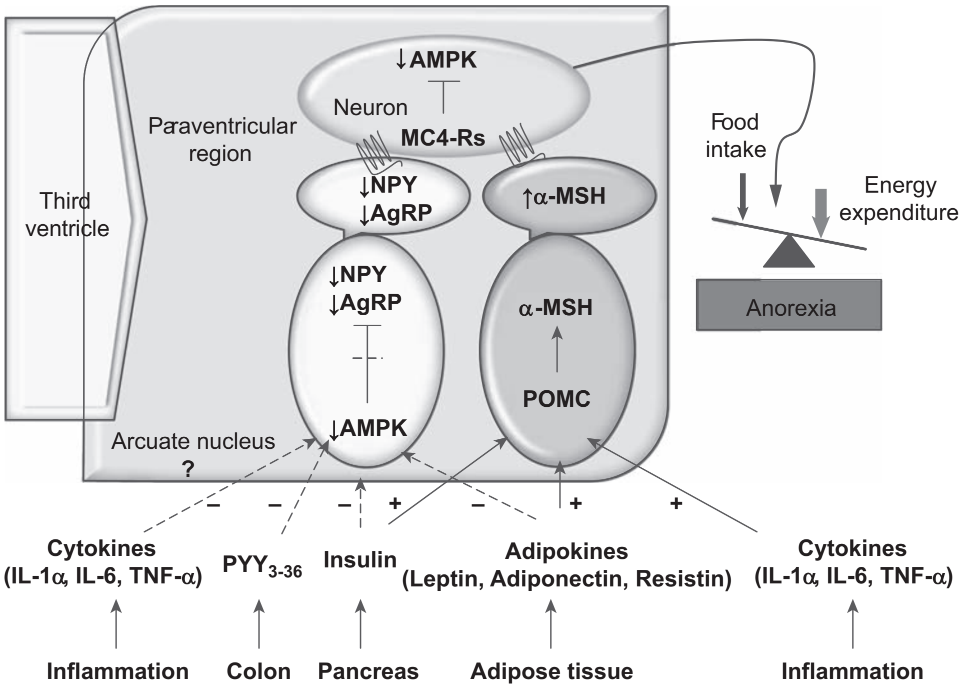

FIGURE 13.2 Orexigenic and anorexigenic mechanisms controlling energy homeostasis in CKD. Circulating hormones produced by the colon (PYY), pancreas (insulin) adipose tissue, and cytokines all cause anorexia. Responses to these factors result in the modulation of the hypothalamic melanocortin signaling pathways with an increase in MC4-Rs that suppresses AMPK activity, leading to decreased food intake, increased energy expenditure, and weight loss. *AMPK*, AMP-activated protein kinase; *CKD*, chronic kidney disease; *PYY*, peptide YY [45]. Source: *Reprinted with permission from Mak RH, Cheung W, Cone RD, Marks DL. Orexigenic and anorexigenic mechanisms in the control of nutrition in chronic kidney disease. Pediatr Nephrol 2005;20:427–31.*

correlated with worse malnutrition–inflammatory scores [56]. It is speculated that the apparent unfavorable effect of high adiponectin might not necessarily be related to a direct effect of adiponectin, but rather it could be a consequence of a concurrent process of wasting with a secondary increase in adiponectin levels [57].

Effect of volume overload

Chronic volume overload and concomitant heart failure are frequent complications of CKD. There is increasing evidence that fluid volume overload may contribute to malnutrition in CKD patients that may contribute to PEW. For instance, volume overload is associated with inadequate dietary protein and energy intake [58] and nutritional status in maintenance PD patients [59]. In a large cohort of ESRD patients undergoing renal replacement therapy, plasma levels of the N-terminal fragment of B-type natriuretic peptide (NT-proBNP) and the extracellular fluid volume/total body water (ECFv/TBW) ratio were correlated with several markers of inflammation and poor nutrition [60,61]. Furthermore, chronic fluid overload, as measured by multifrequency bioimpedance analysis, is significantly correlated with markers of malnutrition, inflammation, and atherosclerosis among PD patients [62]. These data suggest that there may be a link between the malnutrition–inflammatory state and hypervolemia in patients with CKD.

Contribution of comorbidities

A number of comorbid diseases or conditions that are prevalent in ESRD patients may also contribute to PEW in such patients [4,63]. These include diabetes, hypertension, atherosclerosis, chronic heart failure, intercurrent catabolic illnesses such as infections, and advanced age. In addition to the hyperglycemia and insulin-resistant state in diabetes, other comorbid disorders related to diabetes, including gastrointestinal dysfunction, hypertension ischemic vascular disease, and neuropathy, may reduce food intake and add to protein wasting in CKD patients. Patients with CKD frequently sustain acute intercurrent illnesses that may also reduce food intake and induce a negative nitrogen balance. In addition, many patients with ESRD have evidence of atherosclerotic cardiovascular disease (CVD) that is associated with malnutrition or PEW and increased levels of proinflammatory cytokines [4]. Because of the strong associations between malnutrition, inflammation, and atherosclerosis in CKD, it has been proposed that these features constitute a specific syndrome termed "malnutrition–inflammation–atherosclerosis", which carries a high mortality rate.

Altered protein kinetics in chronic kidney disease

An increase in net proteolysis due to imbalance between protein synthesis and degradation has been reported in uremic animals [64]. The results from the human studies, however, are more controversial than those from animal studies. Muscle and whole-body protein turnover studies in stable advanced CKD/ESRD patients have consistently shown that there is a balanced reduction in protein synthesis and degradation, such that there is no net protein loss [65–67]. On the other hand, investigators unanimously agree that HD induces protein catabolism. Lim et al. [68] reported normal basal leucine flux, a transient decrease in protein synthesis and a negative protein balance during HD. Ikizler [69] found that protein catabolism is increased during HD, with no significant change in protein synthesis. Using multiple tracers, Raj et al. [67] observed a significant increase in both protein synthesis and breakdown during HD. However, the intradialytic increase in catabolism exceeded that of synthesis, resulting in net muscle protein loss.

Albumin is a negative acute-phase protein, and fibrinogen is a positive acute-phase protein. In healthy humans, albumin and fibrinogen account for ~50% and ~10% of the total liver protein synthesis, respectively. The changes in albumin, fibrinogen, and muscle protein synthesis rates vary according to the pathophysiological state. For instance, albumin and fibrinogen synthesis rates increase in nephrotic syndrome [70]. However, in inflammatory states, the synthesis rates for albumin, fibrinogen, and muscle protein may show a concomitant increase or they may be discordant depending on the cause, intensity, and duration of inflammation [71,72]. Giordano et al. [73] reported that synthesis rates of albumin and fibrinogen are increased in ESRD patients with normal nutritional status. Kaysen et al. found that albumin synthesis is lower in hypoalbuminemic ESRD patients, and that albumin synthesis and catabolism in ESRD are modulated by inflammation [74,75]. Caglar et al. [76] observed that the intradialytic increase in albumin synthesis rate (64%) was higher than that of fibrinogen (34%), but Raj et al. [77] noted that the fractional synthesis rate of fibrinogen (53.5%) tended to be larger than that of albumin (38.6%) during HD. Thus protein catabolism appears not to be increased, even in advanced CKD, in the absence of other superimposed illnesses.

PD treatment provides 300–600 kcal/day primarily from absorption of glucose from the use of dextrose-based dialysis solutions resulting in hyperinsulinemia in these patients. Goodship et al. [78] performed leucine turnover studies in CKD patients before and after 3 months of continuous ambulatory PD (CAPD) treatment. They observed that protein turnover was decreased at baseline, but the balance between synthesis and breakdown was higher and remained unchanged after 3 months on CAPD. Long-term use of amino acid–based PD fluid has been shown to induce a positive protein balance [79]. About 80% of leucine contained in the dialysate solution is absorbed through peritoneum and about 43% of the leucine absorbed is used for protein synthesis [80].

Nutrient loss during dialysis

Chronic blood loss and losses of several nutrients, including glucose, amino acids, peptides, and proteins, as well as water-soluble vitamins during the dialysis may contribute to the pathogenesis of PEW in ESRD patients. Raj et al. [81] studied the alanine and glutamine kinetics in ESRD patients using a three compartmental model (artery, vein, and muscle) and showed that the intracellular amino acid concentration is maintained during HD by muscle protein catabolism. However, they noted that amino acid infusion during dialysis increased muscle protein turnover, with a balanced increase in both protein synthesis and breakdown [82]. On the other hand, Pupim et al. [83] demonstrated that intradialytic parental nutrition increases whole-body protein synthesis and decreases proteolysis. Forearm muscle protein kinetics, however, showed that while protein synthesis is increased, protein breakdown is unchanged. Thus it appears that amino acid repletion increases protein synthesis without a significant impact on muscle protein catabolism.

Inflammation: agent provocateur of protein-energy wasting

A large body of evidence indicates that inflammation plays a central role in the pathogenesis of PEW in CKD beyond its role in protein catabolism. For example, cytokines, such as tumor necrosis factor (TNF)-α, interleukin (IL)-1, and IL-6, can cause anorexia by acting on the central nervous system via modulation of the melanocortin signaling system to alter the release and function of several key neurotransmitters that regulate appetite and metabolic rate (Fig. 13.3). IL-1 has been shown to inhibit gastric emptying, an effect mediated in part by CCK release.

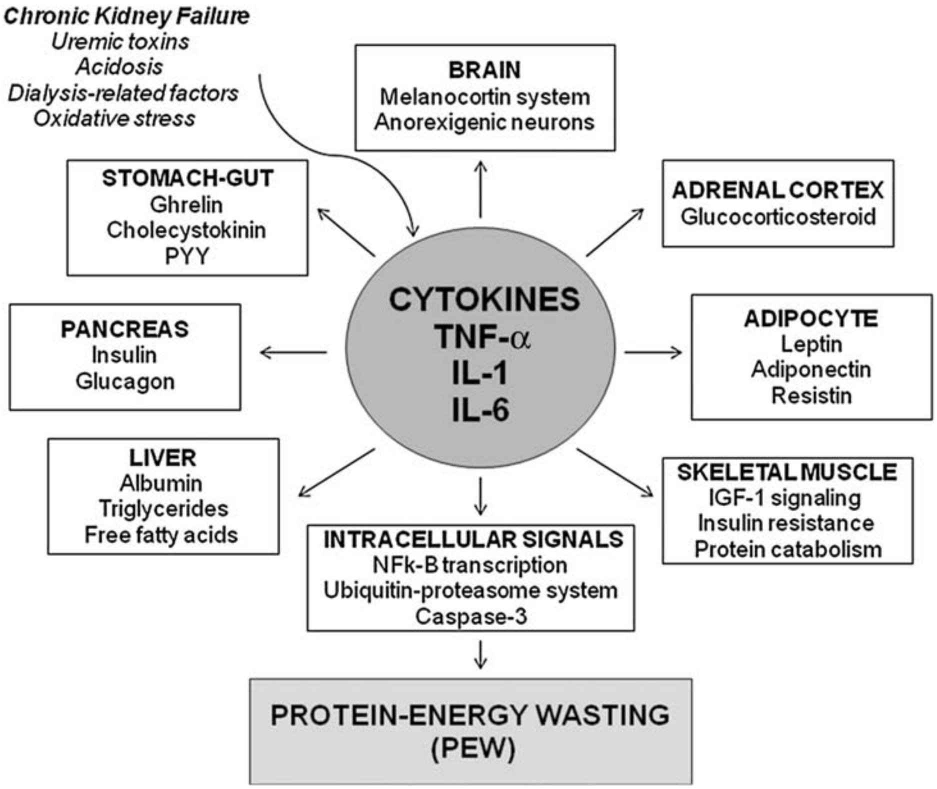
Chronic Kidney Failure
Uremic toxins
Acidosis
Dialysis-related factors
Oxidative stress
BRAIN
Melanocortin system
Anorexigenic neurons
STOMACH-GUT
Ghrelin
Cholecystokinin
PYY
ADRENAL CORTEX
Glucocorticosteroid
CYTOKINES
TNF-α
IL-1
IL-6
PANCREAS
Insulin
Glucagon
ADIPOCYTE
Leptin
Adiponectin
Resistin
LIVER
Albumin
Triglycerides
Free fatty acids
SKELETAL MUSCLE
IGF-1 signaling
Insulin resistance
Protein catabolism
INTRACELLULAR SIGNALS
NFk-B transcription
Ubiquitin-proteasome system
Caspase-3
PROTEIN-ENERGY WASTING
(PEW)

FIGURE 13.3 Central role of cytokines in the pathophysiology of protein-energy wasting in CKD. *CKD*, Chronic kidney disease.

It is becoming increasingly clear that intradialytic loss of amino acids, and the resultant deficiency of amino acids, is only a part of the paradigm, the other being cytokine activation facilitating augmented protein catabolism [84]. Besides peripheral blood mononuclear cells, human skeletal muscle cells appear to have the inherent ability to express a variety of cytokines [85,86]. Muscle-derived IL-6 functions as an exocrine hormone, exerting its effects on the liver and adipose tissue. Raj et al. [85] demonstrated that cytokines are released from the muscle into the vein during HD. Furthermore, they showed that IL-6 leads to activation of genes promoting protein catabolism [87], efflux of amino acids from the muscle [82] and increased synthesis of hepatic acute-phase proteins during HD [88] (Fig. 13.4). The same group of investigators observed that caspase-3 activity in the skeletal muscle, accumulation of 14-kDa actin fragment (a measure of muscle protein breakdown), and apoptosis are increased during HD [89]. Muscle protein catabolism was positively associated with caspase-3 activity and skeletal muscle IL-6 content. These findings suggest that muscle atrophy in ESRD may also be caused by IL-6-induced activation of caspase-3 resulting in apoptosis as well as muscle proteolysis during HD (Fig. 13.5).

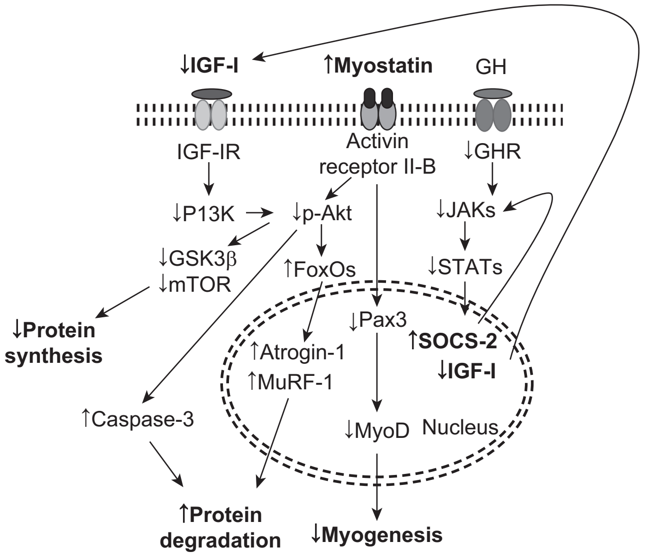
↓IGF-I
↑Myostatin
GH
IGF-IR
Activin receptor II-B
↓GHR
↓P13K
↓p-Akt
↓JAKs
↓GSK3β
↓mTOR
↑FoxOs
↓STATs
↓Protein synthesis
↓Pax3
↑SOCS-2
↓IGF-I
↑Atrogin-1
↑MuRF-1
↑Caspase-3
↓MyoD
Nucleus
↑Protein degradation
↓Myogenesis

FIGURE 13.4 Pathophysiology of muscle wasting in CKD. IGF-I increases muscle mass while myostatin inhibits its development. Muscle wasting could be due to imbalance of this regulation. PI3K activity is key to activation of muscle proteolysis through regulation of caspase-3 and expression of atrogin-1/MAFbx. *CKD*, Chronic kidney disease; *IGF*, insulin-like growth factor; *PI3K*, phosphatidylinositol 3 kinase [90]. Source: *Reprinted from Cheung WW, Rosengren S, Boyle DL, Mak RH. Modulation of melanocortin signaling ameliorates uremic cachexia. Kidney Int 2008;74:180–86.*

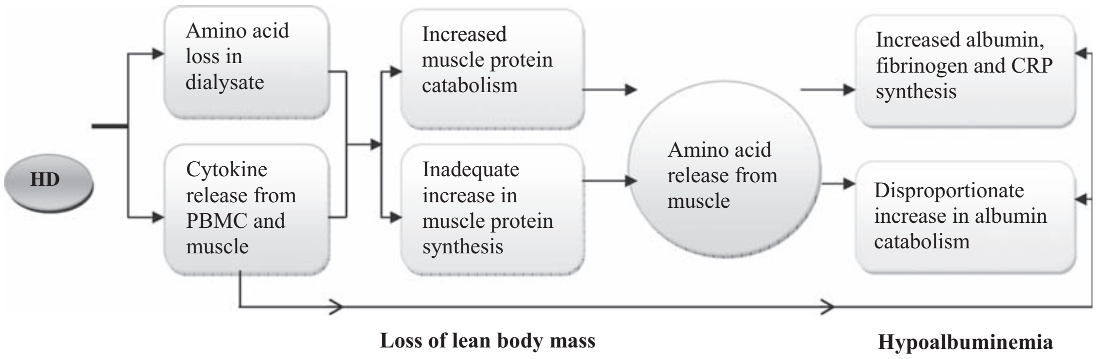
HD
Amino acid loss in dialysate
Cytokine release from PBMC and muscle
Increased muscle protein catabolism
Inadequate increase in muscle protein synthesis
Amino acid release from muscle
Increased albumin, fibrinogen and CRP synthesis
Disproportionate increase in albumin catabolism
Loss of lean body mass
Hypoalbuminemia

FIGURE 13.5 Integrating cytokine, amino acid kinetics, and protein turnover in ESRD. Activation of cytokines during HD increases synthesis of acute-phase protein, which is probably facilitated by constant delivery of amino acids derived from the muscle catabolism and intradialytic increase in IL-6 [77]. *ESRD*, End-stage renal disease; *HD*, hemodialysis; *IL*, interleukin.

Role of metabolic acidemia

The National Kidney Foundation Kidney Disease and Dialysis Outcome Quality Initiative guidelines maintain a serum bicarbonate level in ESRD patients of at least 22 mEq/L. Accordingly, in cohort studies, a serum bicarbonate level of >22 mEq/L was associated with lower death risk among ESRD patients [91] and higher bicarbonate concentration was also associated with lower mortality among patients with nondialysis-dependent CKD [92]. Catabolic effects of metabolic acidemia may result from an increased activity of the adenosine triphosphate–dependent ubiquitin-proteasome and branched-chain amino acid oxidation [93]. In addition to its effects on PEW and associations with poorer survival, academia may also have deleterious effects on kidney function and may be a risk factor for progression of CKD [94,95]. There may be advantages to increase the arterial pH beyond simply reaching the lower limit of the reference range. In a randomized, crossover metabolic balance study of eight ESRD patients treated with PD, increasing the arterial pH from 7.38 to 7.44 resulted in significantly higher net positive nitrogen balances in all but one patient [96]. Although a few single-center studies have showed that bicarbonate supplementation in patients with CKD improved nutritional status, a recent metaanalysis found no significant benefit of oral alkali supplementation on nutritional assessments in patients with CKD [97]. The potential benefits of alkali therapy on nutritional status have to be balanced with possible adverse effects related to the inadvertent development of alkalemia [98].

Oxidative stress: other key pathways

CKD is characterized by activation of the renin–angiotensin system. Interestingly, angiotensin II infusion has been shown to induce skeletal muscle atrophy, which was associated with oxidative stress, increased expression of the E3 ligases atrogin-1/MuRF-1, and augmented ubiquitin proteasome–mediated proteolysis [99,100]. Several lines of evidence link reactive oxygen species (ROS) to muscle atrophy via redox control of proteolysis [101]. Arteriovenous balance studies have shown net release of malonaldehyde and carbonyl protein from skeletal muscle during HD indicating increased generation of ROS. Thus increased oxidative stress could contribute to muscle wasting in CKD.

Nuclear factor-κB (NF-κB) is at the interface between oxidative stress and inflammation and is activated during HD [86]. NF-κB inhibits myogenesis by promoting myoblast growth and inducing loss of MyoD, which stimulates skeletal muscle differentiation and repair [102] (Fig. 13.4). In HD patients the expression of NF-κB has been shown to be negatively correlated with creatinine index, serum albumin, and percentage body fat [103]. In addition, restoring the activity of nuclear factor-erythroid 2-related factor 2 (Nrf2), which is a master regulator of antioxidant genes and is suppressed by NF-κB, has been suggested as a potential therapeutic strategy to reduce oxidative stress and inflammation in CKD [104]. Another molecule, myostatin, a member of the transforming growth factor-β superfamily of signal transduction proteins, is an important regulator of skeletal muscle mass and repair [105,106]. Systemic overexpression of myostatin in adult mice was found to induce profound muscle and fat loss analogous to that seen in human cachexia syndromes [107]. Verzola et al. [108] observed that myostatin gene expression is increased in the skeletal muscle of patients with CKD. Thus it appears that activation of multiple pathways distinct and yet interrelated signals mediate muscle atrophy in patients with CKD.

Treatment of protein-energy wasting in chronic kidney disease

Since the etiology of PEW in patients with CKD is complex and multifactorial, a multidisciplinary, multifaceted, and individualized approach is required to prevent or reverse the PEW in CKD. These include optimizing dietary nutrient intake, appropriate treatment of metabolic disturbances such as metabolic acidosis, systemic inflammation, and hormonal deficiencies, and prescribing optimized dialytic regimens [109]. If these standard preventive measures are unable to effectively diminish the loss of protein and energy stores, additional therapeutic strategies need to be considered.

Nutritional supplementation

Nutritional supplementation is generally recommended as the first step of nutritional support when dietary counseling and standard preventive measures are not sufficient to achieve the planned nutritional requirements [110]. The indications for the treatment of PEW in patients with CKD recommended by the ISRNM are summarized in Table 13.3 [109]. Oral supplementation should be given two to three times a day, preferably 1 hour after main meals or during dialysis for maintenance HD patients. It can provide an additional 7–10 kcal/kg per day of energy and 0.3–0.4 g/kg per day of protein over a minimum spontaneous intake (i.e., 20 kcal/kg per day of energy and 0.4–0.8 g/kg per day of protein) to meet the recommended dietary energy and protein intake targets [103]. The studies investigating the effects of oral nutritional supplementation (e.g., oral amino acid tables) on the overall nutritional status of HD patients with PEW have yielded encouraging results, showing the improvement of various nutritional parameters such as albumin concentration and lean body mass [111,112]. Moreover, oral nutritional supplementation might have beneficial effects on patient's quality of life, physical functioning, hospitalization rates, and overall survival [113–116].

Although feeding through the gastrointestinal route is preferred for nutritional supplementation, feeding through the parenteral route [i.e., total parenteral nutrition (TPN)] can be considered a safe and convenient approach for patients who cannot tolerate oral or enteral administration of nutrients [109]. In patients on maintenance HD, parenteral nutrition can be conveniently administered during HD treatment via the dialysis tubing [a.k.a. intradialytic parenteral nutrition (IDPN)], which is a significant advantage by eliminating the need for an additional venous catheter placement. In a prospective, randomized, controlled, French Intradialytic Nutrition Evaluation (Fine) study, similar beneficial effects on nutritional status have also been observed for IDPN plus oral supplements (vs oral supplements alone) in HD patients [117]. It is important to note that IDPN should be used as a supplement and not a sole source of nutrients (i.e., it cannot be used as TPN), as in itself it is insufficient to satisfy all the nutrient needs of an individual. According to the results from Fine study, only 6.4 kcal and 0.25-g protein/kg per day were additionally delivered through IDPN plus oral supplements in HD patients [117].

Exercise

Decreased physical activity plays a major role in the pathophysiology of PEW. Physical activity has been reported to be severely reduced in maintenance HD patients [118,119]. It has been increasingly recognized that regular physical activity improves cardiac function, enhances muscular strength, and increases exercise capacity in patients with CKD [120]. A recent metaanalysis has shown that progressive resistance training not only increases muscular strength accompanied by skeletal muscle hypertrophy but also improves health-related quality of life in CKD patients [121]. Resistance training has been proven safe, feasible, and well tolerated in various clinical settings, including outpatient clinic, home-based regimes, and programs concomitant to dialysis [40]. In addition, a recent study provided compelling evidence that

TABLE 13.3 Indications for nutritional interventions in chronic kidney disease (CKD) patients.

- Poor appetite and/or poor oral intake
- DPI <1.2 (CKD stage 5D) or <0.7 (CKD stages 3 and 4)
- DEI <30 kcal/kg/day
- SAlb <3.8 g/dL or SpreAlb <28 mg/dL
- Unintentional weight loss >5% of IBW or EDW over 3 months
- Worsening nutritional markers over time
- SGA in PEW range

DEI, Dietary energy intake; *DPI*, dietary protein intake; *EDW*, estimated dry weight; *IBW*, ideal body weight; *PEW*, protein-energy wasting; *SAlb*, serum albumin; *SGA*, subjective global assessment; *SPreAlb*, serum prealbumin.

Adapted from Ikizler TA, Cano NJ, Franch H, et al. Prevention and treatment of protein energy wasting in chronic kidney disease patients: a consensus statement by the International Society of Renal Nutrition and Metabolism. Kidney Int 2013;84:1096–107.

regular moderate-intensity aerobic exercise such as walking is safe with regard to immune and inflammatory responses and has the potential to be an effective antiinflammatory therapy in CKD patients [122]. Although studies in ESRD patients have not demonstrated consistent long-term beneficial effects of exercise on clinically relevant outcomes such as improvements in muscle strength and physical functioning, the combination of exercise with nutritional supplementation, along with adequate intensity and/or duration of exercise, may serve as a potential countermeasure for PEW in ESRD [123].

Pharmacological interventions

Several pharmacological agents have emerged as additional approaches for the treatment of PEW in CKD. These include anabolic agents (e.g., testosterone, GH), appetite stimulants, and antiinflammatory agents.

Anabolic steroids

Anabolic steroids stimulate net muscle protein synthesis by inducing mRNA expression of skeletal muscle androgen receptor and increasing the intracellular pool of amino acids derived from protein degradation [124]. Administration of supraphysiologic doses of testosterone, especially when combined with strength training, has been shown to increase lean body mass and muscle size and strength in patients with various disease conditions [125–127]. Several randomized controlled trials in both male and female HD patients showed that treatment with nandrolone decanoate significantly increased both anthropometric and biochemical parameters, including body weight, body mass index, skinfold, midarm muscle circumference, and serum levels of total protein, prealbumin, and transferrin [128–130]. In addition, treatment with the androgenic steroid oxymetholone has been shown to be associated with an increase in fat-free mass, handgrip strength, and muscle mRNA levels for several growth factors, together with a decrease in fat mass [131]. It is important to note that the use of anabolic steroids should be limited to 6 months due to their potential side effects [109].

Recombinant human growth hormone

Administration of recombinant human GH (hGH) has been shown to increase linear growth in children with CKD and improve net protein balance in malnourished adult ESRD patients on maintenance HD [132]. A number of detailed metabolic studies and prospective randomized trials provide convincing direct or indirect evidence that GH treatment can improve not only nutritional biomarkers and lean body mass, but also inflammation, lipid profile, erythropoiesis, and cardiovascular status in maintenance dialysis patients [109]. Beneficial effects of GH on net muscle protein balance are believed to be due to a combination of simultaneous improvements in protein synthesis and protein breakdown, suggesting a potential involvement of multiple mechanisms, such as direct actions of GH on protein synthesis and indirect actions through activation of IGF-I [40]. Although recombinant hGH is currently not commonly used to treat PEW in patients with CKD, these hormones represent a potentially effective intervention in this vulnerable patient population [40,133–136]. In the OPPORTUNITY Trial, a randomized clinical trial examining the efficacy and safety of once-daily subcutaneous injections of hGH (vs placebo) in adult hypoalbuminemic maintenance HD patients, treatment with hGH improved certain cardiovascular risk factors, including reduced total fat mass, increased serum high-density lipoprotein cholesterol and transferrin, and reduced serum high-sensitivity C-reactive protein and possibly homocysteine. OPPORTUNITY was terminated early after randomizing only 712 of the planned 2500 patients. In this smaller group of patients the administration of hGH did not reduce mortality, cardiovascular events or improve nutritional factors or quality of life [133]. In another study investigating the potential additive anabolic effects of hGH plus human IGF-I (hIGF-I) in HD patients, a short-term administration of a moderate dose of hGH plus hIGF-I (vs hIGF-I alone) significantly improved whole-body protein synthesis [134].

Appetite stimulants

Pharmacologic agents that may stimulate appetite include megestrol acetate, dronabinol, cyproheptadine, melatonin, thalidomide, and ghrelin. Most of these drugs, however, have not been systematically studied in HD patients with PEW. Megestrol acetate, a progesterone derivative, can stimulate appetite and induce small increases in serum albumin and weight in HD patients [137]. Ghrelin is an orexigenic peptide released primarily from the stomach that increases appetite and adjusts both short- and long-term energy balance. In addition to its direct orexigenic effects (as aforementioned), ghrelin administration has been shown to inhibit sympathetic nerve activity and inflammatory response and improve left ventricular function and exercise capacity [109], making it a potentially promising drug candidate for the treatment of PEW in patients with ESRD.

Antiinflammatory agents

Antiinflammatory agents could be considered for the treatment of PEW in CKD patients who are persistently inflamed despite appropriate interventions for potential sources of inflammation (e.g., infections, fluid retention) [138]. Such agents include the drugs that have pleiotropic antiinflammatory effects and anticytokine agents [138,139]. Commonly used drugs in CKD such as statins, vitamin D receptor agonists, and angiotensin-converting enzyme inhibitors have been shown to possess antiinflammatory properties [138,139]. Although these drugs are seldom prescribed with the sole intention of reducing inflammation and are in fact not as effective as antiinflammatory agents, they are often considered valuable adjuvants in strategies aiming at reducing systemic inflammation in CKD patients [138,139]. Currently, there are only limited studies on the effects of anticytokine agents on nutritional parameters in uremic patients. In a small pilot study of 22 HD patients, administration of IL-1 receptor antagonist resulted in significant improvements in C-reactive protein and IL-6 levels, along with an increase in serum albumin, serum prealbumin, and lean body mass [140]. Similarly, the administration of etanercept, a TNF receptor antagonist, showed positive effects on serum albumin and prealbumin levels in HD patients [141]. Pentoxifylline, a nonspecific phosphodiesterase inhibitor, is another anticytokine agent that inhibits the production of TNF, IL-6, and IL-10 [142]. In patients with CKD the administration of pentoxifylline has been shown to improve protein breakdown along with an incremental anabolic effect when combined with a balanced amino acid mixture [143]. In a recent randomized controlled trial of 36 HD patients, pentoxifylline administration for 4 months significantly reduced serum concentrations of inflammatory biomarkers [144], suggesting its therapeutic potential for PEW in CKD. It should be noted, however, that the antiinflammatory treatment with these biological anticytokine agents may increase the risk of infections and other complications such as severe allergic reactions. Therefore large-scale studies are needed to examine the efficacy and safety of anticytokine therapies as nutritional interventions in CKD patients.

Antimyostatin agents

Pharmacological inhibition of myostatin has been suggested as a new therapeutic choice for PEW in CKD [106]. In CKD mice, subcutaneous injections of an antimyostatin peptibody (a chimeric peptide-Fc fusion protein) suppressed circulating inflammatory cytokines and reversed the loss of body weight and muscle mass [145]. These effects were associated with decreased muscle protein degradation and increased protein synthesis, as well as enhanced satellite cell function and IGF-I signaling [145]. In a recent study using a rodent CKD model, myostatin inhibition via a neutralizing peptibody suppressed the proliferation of newly identified fibro/adipogenic progenitor cells and muscle fibrosis [146]. In humans, myostatin-targeted therapeutic approaches have been studied in early stage clinical trials in a variety of conditions, including genetic disorders, cachexia syndromes, and disuse, and demonstrated increase in muscle mass and functional measures of muscle [147–150]. However, it remains unknown whether these antimyostatin agents can exert similar beneficial effects for PEW in patients with CKD.

Summary and conclusion

There is an increasing incidence and prevalence of CKD worldwide with poor outcomes and profound economic implications. CVD is the most common cause of death in patients with CKD. Conventional risk factors of CVD and mortality (obesity, serum cholesterol, and homocysteine) may paradoxically have a protective effect in ESRD patients suggesting that nutritional status has an overriding effect on survival [151–153]. Surveys using classic measures of nutritional status indicate that approximately 20%–75% of CKD patients show evidence for malnutrition or wasting [154]. Results from the National Health and Nutrition Examination Survey III confirm that renal function is independently associated with PEW [155]. CKD patients have clinical and biochemical evidence of PEW such as anorexia, loss of lean body mass, decreased serum albumin, prealbumin and IGF-I, impaired response to anabolic hormones, ineffective amino acid utilization for protein synthesis, and increased energy expenditure, especially in the setting of coexistent inflammation. The pathogenesis of PEW in CKD is multifactorial and involves a complex interplay of several factors or mediators that directly or indirectly affect nutrient intake, protein metabolism, and energy balance, which may vary in importance depending upon the nature of the inciting stimulus or event that occurs during the evolution of the disease. It is clear that factors, such as anorexia with inadequate food intake, acidemia due to advanced renal failure, and nutrient losses into dialysate in dialysis patients, play a contributory role. More recently, identified mediators of PEW include proinflammatory cytokines, insulin resistance, abnormal neuroendocrine signaling, altered physiology of adipokines, and abnormal skeletal muscle protein kinetics. A clear understanding of the pathogenic mechanism and cellular signaling pathways is important to institute individualized, targeted interventions for PEW in CKD.

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CHAPTER

14

Prevention and management of cardiovascular disease in kidney disease and kidney failure

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Introduction

Cardiovascular disease (CVD) is the leading cause of morbidity and mortality in persons with chronic kidney disease (CKD) and accounts for over 50% of deaths in patients with end-stage kidney disease (ESKD) [1]. CKD is a powerful risk state for the development of coronary artery disease (CAD), leading the National Kidney Foundation and the American College of Cardiology/American Heart Association (ACC/AHA) to recommend that CKD be considered a CAD risk equivalent [2,3]. While traditional cardiovascular risk factors, such as smoking, hypertension, diabetes, dyslipidemia, and older age, are more prevalent in patients with CKD than the general population, a number of nontraditional risk factors, including oxidative stress and inflammation, protein-energy wasting (PEW), anemia, fluid overload, and arterial calcification, may also contribute to the increase in morbidity and mortality in this population (Box 14.1) [3].

In this chapter, we discuss the epidemiology of cardiovascular risk factors, including hypertension, dyslipidemia, diabetes, left ventricular hypertrophy (LVH), and PEW, in the setting of kidney disease. In addition, we review strategies to prevent and manage coronary disease and heart failure (HF) in dialysis patients as well as patients with CKD stages 3 and 4. The care of kidney transplant recipients, diagnostic cardiovascular testing, the use of specific biomarkers, and other CVD outcomes, such as stroke, peripheral artery disease, and pericardial and valvular diseases, are beyond the scope of this chapter (see Chapter 33 for information about nutritional management of kidney transplant recipients). Details on the mechanisms of PEW, inflammation, uremia, and oxidative and carbonyl stress are covered in Chapters 7, 12, and 13.

Cardiovascular risk factors

Hypertension

Epidemiology: Hypertension is both a cause and result of CKD and its prevalence increases as glomerular filtration rate (GFR) declines [4].

Dialysis

Epidemiology

Depending on the population studied, nearly 85% of dialysis patients have hypertension [5,6]. Hypertension is more common at the time of dialysis initiation due to the presence of volume overload. There is also a high prevalence of intradialytic hypotension and sometimes intradialytic hypertension (approximately 10%). Most studies have shown that there is a “U-” shaped relationship between predialysis blood pressure (BP) and both CVD outcomes and all-cause mortality [7–10]. Possible explanations for the association of low BP with adverse outcomes include that low BP may reflect the severity of CVD and PEW [11]. Ambulatory blood pressure monitoring (ABPM) may be an option to guide clinical decision-making in dialysis patients since pre- and postdialysis BP measures vary significantly. In addition, data suggest a closer association between ABPM and clinical outcomes [6,12]. Recent literature has emphasized the importance of assessing volume and the relation of excess volume in promoting both hypertension and adverse outcomes in both CKD and dialysis [13,14].

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BOX 14.1

Traditional and unique cardiovascular disease (CVD) risk factors in persons with kidney disease.

Traditional CVD risk factors

- Male sex
- Hypertension
- Higher LDL cholesterol
- Lower HDL cholesterol
- Diabetes
- Smoking
- Physical inactivity
- Menopause
- Family history of coronary disease
- Left ventricular hypertrophy

CVD risk factors unique to persons with kidney disease

- Anemia
- Abnormal bone mineral metabolism
- Uremia and oxidative inflammation
- Malnutrition and PEW
- RAAS overactivity
- Volume overload
- Electrolyte imbalances
- Albuminuria
- “Under treatment”

HDL, High-density lipoprotein; *LDL*, low-density lipoprotein; *PEW*, protein-energy wasting; *RAAS*, renin−angiotensin−aldosterone system.
Modified from Shastri and Sarnak. Cardiovascular disease and CKD: core curriculum 2010. Am J Kidney Dis 2010;56(2):399−417.

Trials and recommendations

The BP in dialysis pilot study randomized 126 dialysis patients to assess the feasibility and safety of a standardized predialysis systolic BP (SBP) of 110−140 mmHg (intensive arm) versus 155−165 mmHg (standard arm) [15] and evaluate its effect on LVH. On average, patients in the intensive arm had a 10 mmHg lower SBP compared to the control arm (146 vs 156 mmHg) but had a greater risk of recurrent hospitalization, vascular access thrombosis, and intradialytic hypotension, despite an increase in postdialysis weight. There was no change in the primary outcome of LVH between groups. While the 2005 Kidney Disease Outcomes Quality Initiative (KDOQI) guidelines suggest pre- and postdialysis BP goals of <140/90 and <130/80 mmHg, respectively (level C recommendation based on expert opinion), several more recent guidelines have refrained from specific BP targets in dialysis patients [16]. Although metaanalyses and some trials have suggested a benefit with the use of antihypertensive agents in dialysis patients [17,18], both because of heterogeneity and small sample sizes, data supporting specific target BP values and preferred antihypertensive agents remain weak. In contrast to a report from the 2015 European Renal and Cardiovascular Medicine Working Group [19], the Kidney Disease: Improving Global Outcomes (KDIGO) consensus committee concluded that there were insufficient data to develop a new guideline on BP management in dialysis patients [20].

CKD stages 1−4

Epidemiology

The pathogenesis of hypertension in CKD is multifactorial with the major mechanisms thought to be salt and water retention as well as activation of the renin−angiotensin−aldosterone system (RAAS). Hypertension is an independent risk factor for the progression of CKD as well as the development of CVD and BP management targets both these complications.

Trials and recommendations

Individual RCTs as well as metaanalyses of RCTs have demonstrated that the use of RAAS inhibitors reduces the progression of kidney disease in patients with and without diabetes [21−25], particularly in those with proteinuria [23,26,27]. The combined use of angiotensin-converting enzyme inhibitors (ACE-I) and angiotensin receptor blockers (ARBs) decreases proteinuria to a greater extent than either drug alone [28,29]; however, in studies of individuals with mild proteinuria, dual blockade was associated with an increased risk of worsening of kidney function, including progression to ESRD without improvement in CVD outcomes or mortality [28,29]. The large VA NEPHRON-D trial randomized patients with type 2 diabetes, albuminuria, and a GFR between 30 and 89 mL/min per $1.73\ \mathrm{m}^2$ to combination therapy with an ACE-I and ARB or ACE-I and placebo [30]. The trial was terminated early due to an increased incidence of adverse events, including acute kidney injury (AKI) and hyperkalemia in the group receiving dual RAAS blockage.

Over the last decade a number of guidelines on the management of BP in persons with CKD have been published. The 2012 KDIGO BP guideline suggested a BP target of <130/80 mmHg in both diabetes and nondiabetes in individuals with >30 mg/d of albuminuria (or equivalent) and 140/90 mmHg in those with <30 mg/d [31]. The greater the levels of proteinuria, the stronger the grade of the recommendation [32]. On the other hand, the European Society of Hypertension/European Society of Cardiology (ESH/ESC) guidelines [33] and the JNC-8 panel members [34] recommended a target of <140/90 for persons with CKD irrespective of the degree of albuminuria. The SPRINT trial randomized 9361 adults ≥50 years with SBP 130–180 mmHg and elevated cardiovascular risk to goal SBP <120 versus <140 mmHg. Patients with diabetes, stroke, HF, proteinuria >1 g/d, polycystic kidney disease, eGFR < 20 mL/min per 1.73 m^2, and ESRD were excluded [35]. The study showed a 27% lower all-cause mortality and 25% lower cardiovascular end point. Similarly, a subgroup analysis of those with CKD in SPRINT (mean GFR 48 mL/min per 1.73 m^2 and median albuminuria 81 mg/g) demonstrated that intensive BP control resulted in nearly 20% lower risk of all-cause and 28% lower risk of CVD-related mortality [36]. A large metaanalysis of 18 trials of BP lowering in patients with stages 3–5 CKD demonstrated a lower risk of mortality with intensive therapy [37]; however, specific target BP goals could not be conclusively recommended because of significant heterogeneity in the studies included.

After the publication of the SPRINT the ACC/AHA 2017 Hypertension guidelines redefined the hypertension as BP ≥130/80 mmHg and recommended antihypertensive treatment to a BP goal of <130/80 mmHg in patients with CKD and others at increased cardiovascular risk [38]; this is similar to the KDIGO recommendation in 2012. The 2018 ESH/ESC guidelines recommend an SBP of 130–139 mmHg and diastolic BP of 70–79 mmHg for patients with CKD [39]. Little data exist in individuals with CKD stage 5, nondialysis as to the optimal BP target.

Dyslipidemia

Abnormalities in lipoprotein metabolism are common in patients with kidney disease and may vary depending on the stage of kidney disease [40] (Table 14.1). Total cholesterol levels may be normal or low in patients with advanced kidney disease, the latter possibly perhaps reflecting PEW [41].

Dialysis

Epidemiology

Hemodialysis (HD) and peritoneal dialysis (PD) patients have increased levels of triglycerides and lipoprotein-a compared to patients with milder forms of kidney dysfunction, with PD patients, potentially reflecting constant dextrose absorption, having particularly atherogenic lipid profiles. The linear association between increasing levels of cholesterol and CAD-related mortality seen in the general population is less evident in patients with kidney disease. Observational studies have demonstrated a "reverse epidemiology" between total cholesterol levels and mortality in dialysis patients, that is, increased risk at low cholesterol levels. In a study of over 12,000 HD patients receiving lipid-lowering therapies, persons with total cholesterol <100 mg/dL had nearly four times the risk of death compared to those with levels between 200 and 250 mg/dL (Fig. 14.1) [42–45]. There is evidence that malnutrition and chronic inflammation may be effect modifiers on this association [44] with low cholesterol being a surrogate for poor nutritional status.

Trials and recommendations

Two trials, 4D (Die Deutsche Diabetes Dialyse) study, in which HD patients with diabetes and high-serum low-density lipoprotein (LDL) were treated with atorvastatin or placebo, and AURORA (A study to evaluate the Use of Rosuvastatin in subjects On Regular hemodialysis: an Assessment of survival and cardiovascular events) in which HD patients were treated with rosuvastatin or placebo, failed to demonstrate a significant reduction in mortality or other CVD outcomes despite reduction in LDL levels [46,47]. The SHARP (Study of Heart and Renal Protection) trial evaluated the efficacy of simvastatin and ezetimibe compared with placebo in lowering cardiovascular outcomes in 9270 patients with CKD and 3023 patients receiving dialysis [48]. Results for the dialysis subgroup in SHARP do not appear dissimilar from those

TABLE 14.1 Lipid profiles across the spectrum of kidney disease as compared to the general population.

	CKD not on dialysis	Nephrotic syndrome	Hemodialysis	Peritoneal dialysis	Posttransplant
Total cholesterol	↑ or ↔	↑↑	↓ or ↔	↑ or ↔	↑ or ↔
HDL cholesterol	↓ or ↔	↓	↓	↓	↓ or ↔
LDL cholesterol	↑	↑↑	↓	↑	↑
Triglycerides	↑	↑↑	↑	↑↑	↑ or ↔
Lp(a)	↑	↑↑	↑	↑↑	↑ or ↔

CKD, Chronic kidney disease; *HDL*, high-density lipoprotein; *LDL*, low-density lipoprotein; *Lp(a)*, lipoprotein-a.
From Garimella PS, Sarnak MJ. Chapter 23: Dyslipidemia. In: Nephrology secrets. 4th ed. Elsevier; 2018.

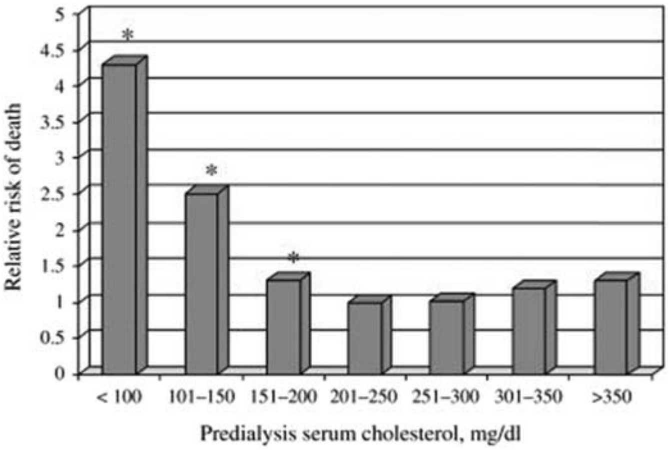

FIGURE 14.1 RR of death in hemodialysis patients according to serum cholesterol concentration compared to the reference group. *RR*, Relative risk. *Source: Reproduced with permission from Lowrie EG, Lew NL. Death risk in hemodialysis patients: the predictive value of commonly measured variables and an evaluation of death rate differences between facilities. Am J Kidney Dis 1990;15(5):458–82.*

seen in 4D or AURORA, showing no significant benefit, although given the absence of a statistical interaction between CKD and dialysis, and a benefit in the entire population, the overall interpretation remains open to debate (Fig. 14.2). Based on the results of the 4D, AURORA, and the dialysis subgroup of SHARP, the 2013 KDIGO guidelines do not recommend initiating statin therapy in persons undergoing HD but suggest continuing them if started prior to the initiation of dialysis. There are no clinical trials focusing on PD, although results from SHARP in the subgroup of participants receiving PD suggest a possible benefit [48].

CKD stages 1–4

Epidemiology

Dyslipidemia is very common in CKD, occurring in over 50% of patients with nephrotic range proteinuria [49]. Like the dialysis population, the presence of malnutrition and inflammation may alter the association between total cholesterol levels and mortality [50].

Trials and recommendations

There is significant controversy surrounding timing of therapy, target LDL level, utility of rechecking levels once medication has been initiated and dose of drug to be used. The best evidence for the use of statins in the prevention of CVD events comes from the SHARP trial in addition to post hoc analysis of trials of the general population. Among 6247 participants with CKD not on dialysis included in SHARP, there was a reduced incidence of CVD mortality, nonfatal myocardial infarction (MI), and stroke (9.5% vs 11.9%) among patients treated with simvastatin and ezetimibe compared to placebo [51]. A metaanalysis of 26 trials that included 25,017 participants with stage 3 or 4 CKD reported a significant reduction in proteinuria, all-cause and cardiovascular mortality, and nonfatal CVD outcomes compared to placebo, without an effect on progression of CKD [52]. In 970 diabetic participants with GFR between 30 and 60 mL/min/1.73 m^2 in the Collaborative Atorvastatin Diabetes Study trial, there was a 42% reduction in major CVD events among patients taking atorvastatin compared to placebo [53]; however, atorvastatin did not reduce mortality similar to the mortality results in SHARP. In the JUPITER trial (Rosuvastatin to Prevent Vascular Events in Men and Women with Elevated C-Reactive Protein), a secondary analysis of patients with CKD (GFR <60 mL/min per 1.73 m^2) demonstrated a 45% reduction in first cardiovascular events and all-cause mortality among men and women with LDL-cholesterol (LDL-C) <130 mg/dL and elevated C-reactive protein (CRP) with rosuvastatin compared to placebo [54].

More recently, a number of drugs targeting proprotein convertase subtilisin/kexin type 9 (PCSK-9) have been studied in the prevention of CVD events. The Long-term Safety and Tolerability of Alirocumab in High Cardiovascular Risk Patients with Hypercholesterolemia Not Adequately Controlled with Their Lipid Modifying Therapy (ODYSSEY LONG TERM) trial enrolled 174 patients with a GFR <60 mL/min per 1.73 m^2 at baseline [55]. In this group, treatment with alirocumab was associated with 62% reduction in LDL-C levels compared to 8% elevation in the placebo arm. While existing data suggest that the benefit afforded by PCSK-9 inhibitors may extend to the earlier stages of CKD [56]. Further studies are needed prior to recommending routine use of PCSK-9 inhibitors in persons with advanced kidney disease.

Based on the abovementioned data, the 2013 KDIGO guidelines recommend screening all persons with CKD not on dialysis using a lipid panel and treating those older than 50 years of age with a statin [57]. In addition, the guidelines recommend treating all patients younger than 50 years of age with known CAD, stroke, and diabetes with a statin. Unlike prior KDOQI guidelines that recommend lowering LDL-C to <100 mg/dL [58], the current KDIGO guidelines do not recommend routine

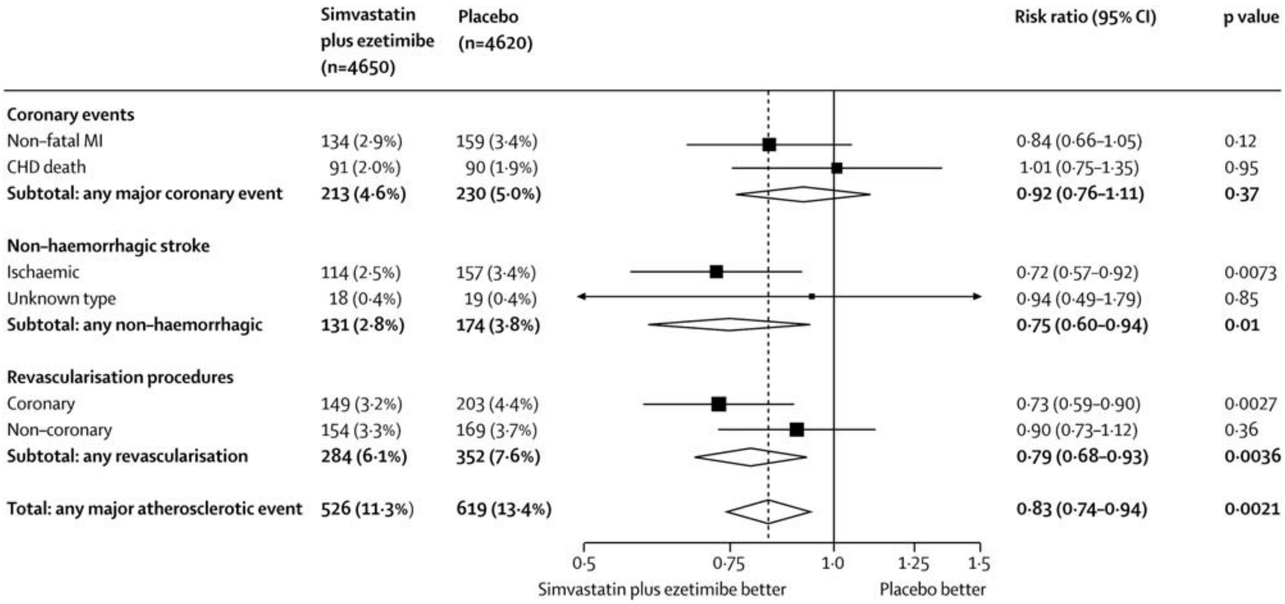

FIGURE 14.2 Major atherosclerotic events subdivided by type. *CHD*, Coronary heart disease; *MI*, myocardial infarction. *Source: Reproduced with permission from Baigent C, Landray MJ, Reith C, Emberson J, Wheeler DC, Tomson C, et al. The effects of lowering LDL cholesterol with simvastatin plus ezetimibe in patients with chronic kidney disease (Study of Heart and Renal Protection): a randomised placebo-controlled trial. Lancet 2011; 377(9784):2181−92.*

follow-up monitoring of lipids in patients taking moderate- or high- intensity statins, defined as daily atorvastatin 20 mg, rosuvastatin 10 mg, simvastatin 40 mg, pravastatin 40 mg, fluvastatin 80 mg, or pitavastatin 2 mg. The treatment of hypertriglyceridemia in CKD is limited by a lack of trial data demonstrating a benefit.

Diabetes mellitus

Diabetes is the most common cause of kidney failure in the United States and is present in approximately 40%−50% of incident dialysis patients [59]. The risk of developing kidney failure among diabetics has declined over the last 20 years, possibly reflecting better glycemic control and use of kidney-protective medications that block the RAAS [59].

Dialysis

Epidemiology

Diabetes is an independent risk factor for all-cause mortality, cardiovascular mortality, and nonfatal CVD events in dialysis patients [60,61].

Trials and recommendations

Post hoc analysis from 4D found that HbA1C values >8% were associated with a twofold increase in sudden cardiac death compared to HbA1C values <6% [62]. However, data from other large observational studies of dialysis patients are conflicting, with some not revealing an association between HbA1C levels and survival in dialysis patients [62−64], while others report a monotonic increase in mortality with higher HbA1C levels, especially in nonanemic patents [65,66]. It is important to recognize that uncontrolled diabetes can worsen retinopathy and diabetic neuropathy and increase the risk of vascular complications, thus necessitating a fine balance to avoid both hyperglycemia and hypoglycemia in this high-risk population. While not perfect, HbA1C seems a reasonable approximation of serum glucose levels in the absence of marked anemia [67]. The 2005 KDOQI guidelines (although outdated) for therapy reflected American Diabetes Association (ADA) recommendations with a target HbA1C of <7% [16]. However, there are no RCTs to support tight control in this population, and we would suggest individual decision-making and tolerance of higher targets in many individuals so as to avoid the risk of hypoglycemia [68]. Extrapolating from studies in populations with high comorbid disease burden, we feel that, in many patients, higher targets are reasonable because of increased risks versus benefits.

CKD stages 1−4

Epidemiology

In patients with CKD, diabetes significantly increases the risk of mortality and adverse CVD outcomes [69]. It had previously been thought that the natural progression of diabetic kidney disease in almost all patients would be microalbuminuria progressing to macroalbuminuria and subsequently to a reduction in GFR. However, it is being increasingly recognized that a significant percentage of patients with presumed diabetic kidney disease develop a sustained decline in GFR without ever developing high levels of albuminuria [70,71].

Trials and recommendations

A number of observational studies have shown that sustained hyperglycemia is a risk factor for the development of moderately elevated urine albumin excretion [72–74], and that a reduction of HbA1C level is associated with a significant decrease in albuminuria and microvascular complications [75,76]. The benefit of strict glycemic control on macrovascular and CVD outcomes is less clear [77]. While some evidence suggests a reduction in cardiovascular mortality among patients with type 1 diabetes mellitus (DM) who maintain near normoglycemia (HbA1C approximately 7%) [78], other trials have shown that intensive glucose control is instead associated with increased mortality and significantly more episodes of hypoglycemia [79,80].

In persons with type 2 DM, results of the ADVANCE Trial showed a 9% reduction in microalbuminuria, 30% reduction in macroalbuminuria, and a 65% reduction in the risk of ESKD with intensive glucose control (achieved HbA1C 6.5%) compared to standard therapy (achieved HbA1C 7.3%) [81]. However, other studies have not shown similar results. Data from the ACCORD (Action to Control Cardiovascular Risk in Diabetes) study that randomized over 10,000 patients who had type 2 diabetes for at least 10 years to an intensive glucose control regimen (target HbA1C <6%) versus regular control (target HbA1C <7%) found an increased risk of all-cause mortality and cardiovascular mortality in the intensive control group [82]. These results question whether tight control is indicated in patients with long-standing diabetes (such as CKD patients). Of note, however, ACCORD excluded participants with frequent or recent serious hypoglycemic events and those with a serum creatinine level of more than 1.5 mg/dL [80]. Critically, post hoc analysis of ACCORD suggests that concurrent intensive BP control and intensive glycemic control may be associated with increased risk of adverse outcomes [83]. The ADA currently recommends maintaining the HbA1C level below 7% but suggests less stringent control in some patients with type 2 diabetes, specifically those with significant comorbid conditions and a reduced life expectancy [84]. Lifestyle and exercise have also been shown to decrease risk of progressive kidney function decline as shown in the Look AHEAD study [85]. In this trial, patients randomized to increased exercise demonstrated slower loss of GFR compared to standard therapy arm.

Sodium–glucose cotransporter-2 (SGLT-2) inhibitors have been approved for use alone or in combination with other agents in individuals with type 2 diabetes [86]. The best evidence of SGLT-2 inhibitor for kidney protection use comes from the CREDENCE (Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation) trial. In CREDENCE, 4401 individuals with type 2 diabetes, severely elevated albuminuria, and eGFR 30– < 90 mL/min per 1.73 m^2 received 100 mg of canagliflozin or placebo added to renin–angiotensin–aldosterone blockade and baseline diabetic therapy [87]. The risk of the primary outcome (composite of ESRD, doubling of serum creatinine, or death from kidney or cardiovascular causes) was reduced by 30% with canagliflozin treatment. Currently, there are no data supporting the initiation of SGLT-2 inhibitors in individuals with GFR <30 mL/min per 1.73 m^2, including dialysis patients, although, in CREDENCE and other SGLT-2 inhibitor trials, these agents were not routinely discontinued when eGFR dropped below 30 mL/min per 1.73 m^2 [88]. Further studies are needed to ensure its safety and efficacy in persons with advanced kidney disease and in persons without diabetes.

Glucagon-like peptide-1 receptor agonists (GLP-1 receptor agonists) are a class of antihyperglycemic drugs that are not cleared by the kidney and, therefore, may confer a lower risk of hypoglycemia compared to insulin in this high-risk population. AWARD-7 was a multicenter trial comparing once-weekly dosing of the GLP-1 receptor agonist dulaglutide to insulin glargine in 577 participants with diabetes and stages 3 and 4 CKD [89]. Treatment with dulaglutide was associated with a lower HbA1C at 26 weeks (primary outcome) and was associated with 2.5 times lower hypoglycemic events compared with insulin glargine. In the LEADER trial, 9340 participants with type 2 diabetes and high cardiovascular risk were randomly assigned to receive liraglutide (a GLP-1 receptor agonist) or placebo, added to standard diabetes treatments. Liraglutide therapy resulted in 22% lower composite kidney outcome (albuminuria, doubling of serum creatinine, ESKD, and mortality) [90] in addition to lowering risk of CVD events in persons with CKD [91].

Left ventricular hypertrophy

LVH is a common complication in all stages of CKD, including dialysis. It represents an adaptation on the part of the myocardium to pressure and fluid overload and is also considered a traditional risk factor for adverse CVD outcomes.

Dialysis

Epidemiology

The prevalence of LVH as detected by echocardiography among incident dialysis patients is reported to be as high as 75% [92–94]. Dialysis patients are host to a number of modifiable risk factors that potentiate the development of LVH, including hypertension, volume overload states, arteriovenous fistulas, and anemia. LVH is an independent risk factor for mortality and adverse CVD outcomes like HF [95–97].

Trials and recommendations

Evidence-based management guidelines for LVH in ESRD and CKD are lacking due to the absence of RCTs. Due to association of LVH with mortality and CV outcomes, the 2005 KDOQI guideline recommended that an echocardiogram be performed in all patients at the initiation of dialysis once patients have achieved dry weight [16]; however, there is no statement of clinical interventions in response to the results of the echocardiogram. Targeting achievement of dry weight and controlling BP are also recommended with indirect evidence in support of these recommendations [98]. Control of hypertension via afterload reduction and optimizing volume status in dialysis patients have shown to be associated with some improvement in LVH. In the Frequent Hemodialysis Network Daily Trial, frequent in-center HD was associated with a composite outcome of lower all-cause mortality and LV mass [99]. However, correction of anemia with erythropoietin has not been shown to prevent or cause regression on LVH in randomized trials [100,101].

CKD stages 1–4

Epidemiology

The prevalence of LVH increases as kidney function declines going from 32% when the GFR is >60 mL/min per 1.73 m^2 to nearly 75% when the GFR is <30 mL/min per 1.73 m^2 [93,102]. LVH is independently associated with worsening kidney function, progression to dialysis, and development of cardiovascular outcomes [103,104].

Trials and recommendations

Despite a number of potentially modifiable risk factors for the development of LVH, success in prevention and regression of established LVH has been limited. The PRIMO trial was a double-blind placebo-controlled trial among 227 patients with CKD and mild-to-moderate LVH. Treatment with paricalcitol did not alter LV mass index or improve parameters of cardiac function in this CKD population [105]. Similar to dialysis, correction of anemia in CKD stages 3 and 4 has not been shown to prevent progression of LVH or worsening of kidney function [106,107] and in some studies has been associated with worsening of cardiac outcomes [108]. Maintaining BP targets and utilization of BP agents as outlined earlier is recommended.

Protein-energy wasting, malnutrition, and inflammation

Epidemiology: The complex syndrome of nutritional deficiency, muscle wasting, and chronic inflammation that occur in persons on dialysis has been given a number of names, including uremic cachexia, malnutrition–inflammation atherosclerosis syndrome, or malnutrition–inflammation complex. The International Society of Renal Nutrition and Metabolism (ISRNM) proposed a common nomenclature and diagnostic criteria for these alterations in the context of CKD. PEW was proposed to denote concurrent losses in protein and energy stores, with cachexia being regarded as only the end stage. PEW may be diagnosed in the presence of at least three of the following four signs: [1] low serum albumin, transthyretin (prealbumin), or cholesterol; [2] decreased body mass (low body mass index, unintentional weight loss, or decreased body fat); [3] reduced muscle mass (low midarm muscle circumference or area, decreased creatinine appearance, or recent history of loss of muscle mass); and [4] unintentional low energy or protein intake [109]. The prevalence of PEW varies with the population studied. In a large metaanalysis of 97 studies with nearly 18,000 patients, the reported prevalence was between 60% and 82% among those with AKI, between 11% and 54% for CKD stages 3–5, and up to 80% in patients on maintenance dialysis [110]. PEW in CKD and dialysis patients is associated with impaired quality of life, greater morbidity, and increased cardiovascular mortality, mortality from infection, and total mortality [111]. Hypoalbuminemia, a surrogate marker for malnutrition, has been associated with increased cardiovascular mortality in dialysis patients [112–114]; however, mortality associated with hypoalbuminemia may reflect chronic inflammation rather than exclusively malnutrition [115,116]. Markers of chronic inflammation, such as elevated CRP and interleukin-6, have been associated with increased morbidity and mortality [117–119]. In addition, sarcopenia and lower fat mass, commonly seen in dialysis patients, are associated with increased mortality and morbidity [120,121].

Trials and recommendations: Scoring systems such as Malnutrition–Inflammation Score [122] and the Objective Score of Nutrition on Dialysis [123] have been developed to identify and predict dialysis patients at risk of increased mortality and morbidity, but further studies are needed to see if any interventions to improve these scores will affect clinical outcomes. Low-protein diets (0.6–0.8 g/kg per day) have been recommended for persons with CKD to slow progression of GFR decline while on the other hand much higher dietary protein is recommended for patients on dialysis [124]. Data suggest a potential benefit of oral protein supplementation and parenteral protein supplementation in dialysis patients on lean body mass and serum albumin levels [125]. There is also emerging observational data that these interventions may be associated with lower hospitalization and mortality [126,127]. No large trials have demonstrated a benefit of nutritional supplementation in reducing mortality, CVD outcomes in dialysis patients. The ongoing Health Effects of Oral Protein Supplements in Hemodialysis Patients trial is an open-label cluster randomized trial evaluating the effectiveness of oral intradialytic nutritional supplements on mortality and should provide answers to some of these questions in late 2020 [128].

Other risk factors

Smoking, obesity, and lack of exercise are other traditional risk factors for CVD in CKD patients. Smoking is associated with adverse cardiovascular outcomes in all stages of CKD [129] and also may promote progression of CKD [130,131]. Smoking cessation is associated with a decrease in the risk of CVD outcomes in dialysis patients [132], and all patients, regardless of CKD status, should be encouraged to quit smoking. Obesity, independent of diabetes, is a risk factor for the development and progression of CKD and development of CVD in the earlier stages of CKD [133,134]. Overweight and obese patients in the early stages of CKD should be encouraged to lose weight (details of nutrition and weight loss in CKD are discussed in Chapter 40), and all patients with CKD should be encouraged to exercise at a moderate intensity for 30 minutes most, if not all, days per week [16]. Patients who are not currently physically active should start at very low levels and durations and gradually progress to this recommended level.

Management of CVD

Coronary artery disease

Epidemiology

CAD is a common cause of CVD morbidity and mortality among patients with kidney disease [1]. The prevalence of CAD among incident dialysis patients may be as high as 40% [135]. The incidence of acute coronary syndromes (ACS) among dialysis patients in the United States Renal Data System (USRDS) Dialysis Morbidity and Mortality study was 29 per 1000 patient years, with risk factors for ACS being similar to the general population—older age, male sex, diabetes, and known CAD [136]. In the same study, outcomes for dialysis patients with MI were extremely poor with 50% and 80%, 1- and 3-year mortality rates, respectively. Even after revascularization with coronary bypass grafting (CABG), mortality rates are exceedingly high with arrhythmias being the cause of death in approximately 25% of these patients [137].

Therapy of ischemic heart disease

Medical therapy

Most trials evaluating prevention and treatment of CAD excluded patients with advanced CKD/ESRD and most trials, including participants with advanced CKD, do not report subgroup analysis based on CKD stage [138]. Therefore most recommendations are based either on observational studies in CKD, subgroup analyses of patients with earlier stages of CKD from general population studies, or extrapolation from trials in the general population [139]. As discussed in the sections earlier, the benefit of preventative measures aimed at lowering the risk of CVD, such as aggressive lipid lowering, and blood glucose control remains equivocal in patients with advanced CKD, especially those on dialysis. Despite the adverse prognosis associated with MI in the setting of CKD, standard therapeutic strategies are less rigorously applied to these patients [140]. This may be due to a combination of poor outcomes despite appropriate therapy and an aversion to include patients with advanced CKD in trials given the higher risk of adverse outcomes with some interventions.

Retrospective analysis of patients enrolled in the Dialysis Outcomes and Practice Patterns Study suggested no benefit on mortality but a lower risk of MI in patients on dialysis who were prescribed aspirin [141]. Post hoc analysis from the PLATO trial, which randomized patients with ACS to either ticagrelor or clopidogrel, demonstrated that the ischemic benefit of ticagrelor over clopidogrel was greatest in persons with both diabetes and CKD [142]. No trials have exclusively addressed antiplatelet therapy for secondary prevention of CAD in CKD/ESRD patients, but post hoc analysis of the Hypertension Optimal Treatment (HOT) study demonstrated that the addition of aspirin resulted in fewer adverse CV events; however, this was not statistically significant, possibly due to small sample size [143]. In the absence of active gastrointestinal bleeding, risks and benefits of aspirin therapy should be assessed for all CKD and dialysis patients, especially those with vascular disease, diabetes, and the elderly. The increased bleeding risk in dialysis patients at risk of CVD but without ACS necessitates an individualized approach.

In patients with stable angina, ACE-I and ARBs have similar benefit in CKD subgroups compared to those without CKD [144,145]. However, ACE/ARB should be used with additional caution in patients with advanced CKD given the increased risk of hyperkalemia. Beta-blockers have only been studied to a limited extent in CAD populations with CKD, but there is evidence to suggest that they confer a mortality benefit among CKD patients with CAD, including patients with HF [146,147]. Data also suggest that beta-blockers may reduce all-cause and sudden cardiac death in dialysis patients with ischemic heart disease [148]. Statin therapy is discussed earlier.

Revascularization

Observational data and older clinical trial data suggest that clinical outcomes for CKD patients with ACS are better after revascularization compared to medical management alone [149–151], resulting in a recommendation in 2011 from the American College of Cardiology Foundation/American Heart Association that an early invasive strategy (i.e., diagnostic angiography with intent to perform revascularization) is reasonable in patients with mild and moderate CKD [152]. A patient-level metaanalysis of individuals enrolled in trials compared percutaneous coronary intervention (PCI) versus CABG suggested that CABG significantly reduces the risk of subsequent MI and revascularization without affecting survival in these patients [153]. However, there were few patients with advanced CKD enrolled in this study. Using data from 21,981 patients on maintenance dialysis in the USRDS registry, investigators compared outcomes between patients who received initial coronary revascularization with either CABG or PCI between 1997 and 2009 [154]. The study demonstrated that CABG compared with PCI was associated with significantly lower risks for both death and the composite of death or MI, but is vulnerable to residual confounding. In another analysis of USRDS data, investigators showed that while in-hospital mortality among dialysis patients undergoing CABG was higher than with PCI, long-term survival and repeat coronary revascularization was lower with CABG [154].Taken together, the observational data support the hypothesis that CABG may be superior to PCI for long-term survival in patients receiving dialysis, with the caveat that these data are biased by patients healthy enough to undergo CABG.

In a retrospective propensity matched analysis of patients with advanced CKD and ACS, therapy with drug-eluting stents (DES) did not significantly improve death, MI, or target vessel revascularization compared with bare-metal stents (BMS) at 2 years of follow-up [155] (Table 14.2). A recent large metaanalysis of 31 studies (5 randomized) with 91,817 participants with CKD and CAD suggests significantly fewer all-cause mortality, cardiovascular mortality, MI, target vessel revascularization, and stent thrombosis events with DES compared to BMS with even a lower stent thrombosis rates with second-generation DES [156].

Similar to patients without CKD who have stable CAD, or are asymptomatic, the role of revascularization among similar patients with CKD remains unclear. The ISCHEMIA-CKD trial randomized 777 patients with stable ischemic heart disease (CAD) and eGFR <30 mL/min per 1.73 m^2, including those in dialysis to optimal medical therapy (OMT) versus revascularization plus OMT [157]. Results show that the primary outcome, death or MI at 2.3 years, occurred in 36.4% of the routine invasive group compared with 36.7% of the OMT group ($P = .95$), therefore suggesting that routine invasive therapy failed to reduce its incidence [158].

Heart failure

Epidemiology

HF is among the more frequently diagnosed CVDs in the CKD population. The bidirectional pathophysiological interaction between abnormalities in kidney (sodium and fluid handling) and cardiac function (decreased cardiac output, venous congestion, and reduced perfusion) is often referred to as cardiorenal syndrome. Both the prevalence and incidence of HF are high in patients with kidney disease, especially those with kidney failure [159]. Over 40% of patients receiving dialysis have prevalent HF [1,61], with recent data from the USRDS also demonstrating a prevalence of HF in CKD patients aged 66 and older of approximately 26%, compared to 6% among patients without CKD [159]. Rates of hospitalization and death due to HF are also significantly higher in dialysis patients than in those without kidney disease

TABLE 14.2 Two-year clinical outcomes.

Outcome	DES (*n* = 431)	BMS (*n* = 431)	Rate difference (95% CI)	*P*
Death	39.4% (170/431)	37.4% (161/431)	2.1% (−4.3–8.5)	.5
MI	16.0% (69/431)	19.0% (982/431)	−3.0% (−8.2–2.1)	.5
TVR	13.0% (56/431)	17.6% (76/431)	−4.6% (−9.5–0.3)	.06

BMS, Bare-metal stent; *CI*, confidence interval; *DES*, drug-eluting stent; *MI*, myocardial infarction; *TVR*, target-vessel revascularization.

Reproduced with permission from Charytan DM, Varma MR, Silbaugh TS, Lovett AF, Normand SL, Mauri L. Long-term clinical outcomes following drug-eluting or bare-metal stent placement in patients with severely reduced GFR: results of the Massachusetts Data Analysis Center (Mass-DAC) State Registry. Am J Kidney Dis 2011;57(2):202–11.

[1]. In a large metaanalysis of patients with HF, those with moderate−severe kidney disease or any kidney disease had 2.3 and 1.5 times risk of death compared to those without kidney disease, respectively [160].

Treatment of heart failure

Volume control by ultrafiltration is an extremely important component of HF therapy in dialysis patients [161]. The maintenance of euvolemia can be challenging, with factors like intradialytic hypotension precluding adequate fluid removal. In such patients, limited evidence suggests that switching to more frequent or longer dialysis may improve fluid balance and cardiac function [162]. PD may also represent an underutilized option. Diuretics are used as first-line therapy in the treatment of volume overload and hypertension in persons with kidney disease. Among persons with decompensated HF and kidney disease, a stepped-up diuretic regimen to achieve adequate urine flow has shown to be as efficacious and potentially safer than the use of extracorporeal fluid removal therapies [163] unless there is concomitant kidney failure needing dialysis. As with persons without kidney disease, the use of diuretics, ACE-I or ARB and beta-blockers forms the mainstay of treatment of persons with kidney disease and HF in the setting of reduced ejection fraction (EF) (Fig. 14.3).

Most studies of HF management have unfortunately excluded patients with advanced CKD. As a result, the vast majority of the literature is extrapolated for populations with either moderate (CKD 3a) kidney disease or those without kidney disease. No trials of ACE-I or ARBs focusing on patients with HF and CKD have been performed. Data from subgroup analysis of larger trials of ACE-I, including the CONSENSUS (Cooperative North Scandinavian Enalapril Survival Study) and the SOLVD Treatment (Studies of Left Ventricular Dysfunction Treatment) trial, demonstrate consistent evidence of better outcomes with ACE-I therapy in patients with HF (or LV systolic dysfunction after MI) and CKD stage 3 [164−166]. The Valsartan in Heart Failure Trial randomized 5010 patients with NYHA classes II to IV HF to receive the ARB valsartan or placebo in addition to optimal HF therapy, which included ACE inhibition in >90% of patients. Of them, 58% had a GFR <60 mL/min per

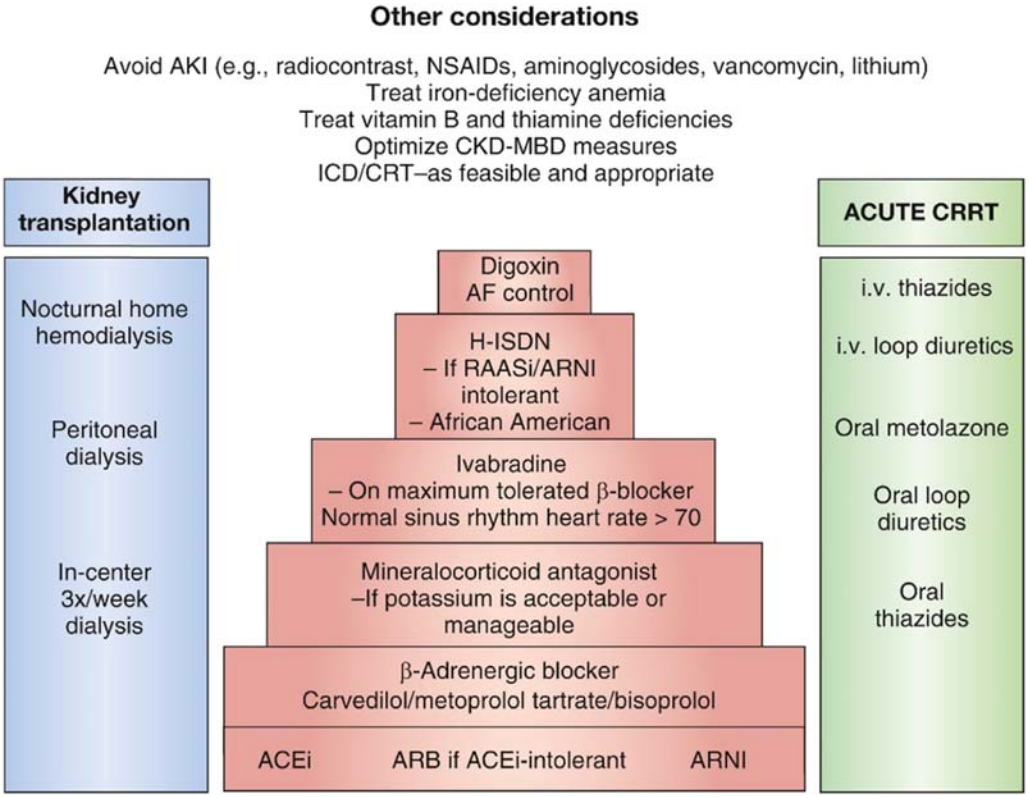
Other considerations
Avoid AKI (e.g., radiocontrast, NSAIDs, aminoglycosides, vancomycin, lithium)
Treat iron-deficiency anemia
Treat vitamin B and thiamine deficiencies
Optimize CKD-MBD measures
ICD/CRT–as feasible and appropriate
Kidney transplantation
Nocturnal home hemodialysis
Peritoneal dialysis
In-center 3x/week dialysis
Digoxin AF control
H-ISDN – If RAASi/ARNI intolerant – African American
Ivabradine – On maximum tolerated β-blocker Normal sinus rhythm heart rate > 70
Mineralocorticoid antagonist –If potassium is acceptable or manageable
β-Adrenergic blocker Carvedilol/metoprolol tartrate/bisoprolol
ACEi
ARB if ACEi-intolerant
ARNI
ACUTE CRRT
i.v. thiazides
i.v. loop diuretics
Oral metolazone
Oral loop diuretics
Oral thiazides

FIGURE 14.3 Pharmacotherapy for the prevention and treatment of heart failure with reduced ejection fraction in CKD progressing to ESKD. *ACE-I*, Angiotensin-converting enzyme inhibitors; *AF*, atrial fibrillation; *AKI*, acute kidney injury; *ARB*, angiotensin receptor blocker; *ARNI*, angiotensin receptor-neprilysin inhibitor; *CKD*, chronic kidney disease; *CRT*, cardiac resynchronization therapy; *ESKD*, end-stage kidney disease; *H-ISDN*, hydralazine−isosorbide dinitrate; *MBD*, mineral bone disease; *RAASi*, renin−angiotensin−aldosterone system inhibitors. *Source: Reproduced with permission from House A.A. et al. Heart failure in chronic kidney disease: conclusions from a Kidney Disease: Improving Global Outcomes (KDIGO) Controversies Conference. Kidney Int 2019;95(6):1304−1317.*

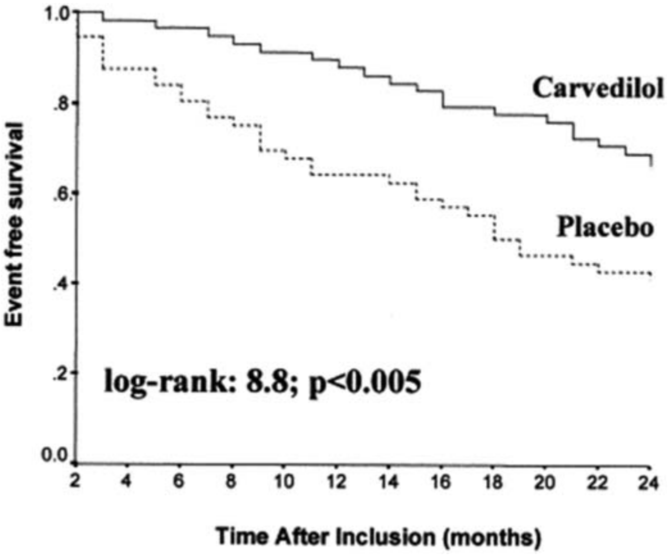

FIGURE 14.4 Kaplan–Meyer curves for all-cause mortality during the 24-month follow-up cumulative survival rate according to the use of carvedilol. *Source: Reproduced with permission from Cice G, Ferrara L, D'Andrea A, D'Isa S, Di Benedetto A, Cittadini A, et al. Carvedilol increases two-year survivalin dialysis patients with dilated cardiomyopathy: a prospective, placebo-controlled trial. J Am Coll Cardiol 2003;41(9):1438–44.*

1.73 m^2 and 8% had dipstick positive proteinuria. The beneficial effect of valsartan on first morbid events was similar in those with and without CKD and proteinuria [166].

Similarly, the beneficial effect of aldosterone blockers in patients with CKD has been demonstrated in post hoc analysis of larger trials. In both the TOPCAT (Treatment of Preserved Cardiac Function Heart Failure with an Aldosterone Antagonist Trial) and the RALES (Randomized Aldactone Evaluation Study) trials, spironolactone therapy was associated with a lower relative risk of outcomes across all eGFR categories, including mortality and HF-related hospitalizations [167,168]. However, in advanced CKD stages, there is a concern for increased risk of hyperkalemia, AKI, and mortality thus warranting closer monitoring. The use of newer potassium binding agents may allow the use of continued RAAS blockage with advanced CKD, which in the past may have been discontinued due to hyperkalemia. In a small trial of patients receiving dialysis, the use of spironolactone was safe and tolerable but did not change diastolic parameters compared to placebo [169].

Finerenone is a newer nonsteroidal mineralocorticoid receptor antagonist that was studied in the Mineralocorticoid Receptor Antagonist Tolerability Study, a dose-finding study in approximately 1000 patients with worsening HF with reduced EF and type 2 DM and/or CKD [170]. All doses of finerenone were associated with a reduction in plasma N-terminal pro–brain natriuretic peptide concentration, while the secondary outcome, including a composite of death, cardiovascular hospitalization, or emergency department visit for worsening HF, occurred less frequently in two highest doses of finerenone-treated patients despite the fact that this phase 2 study was not designed to detect statistical significant differences. Larger studies in more advanced CKD are currently underway [171].

In the MERIT-HF trial, randomized nearly 4000 patients with symptomatic HF and EF $<40\%$ (of which nearly 1500 persons had GFR <60 mL/min per 1.73 m^2), treatment with metoprolol was associated with a greater risk reduction in mortality compared to placebo among persons with CKD than in those without CKD [172]. Similar results were also seen in a study of bisoprolol in persons with kidney disease [173]. Carvedilol is the only beta-blocker to have been studied in a randomized trial in dialysis patients with HF and dilated cardiomyopathy and demonstrated a significant reduction in mortality compared with placebo (Fig. 14.4) [174].

Recently, SGLT-2 inhibitors, including empagliflozin, canagliflozin, and dapagliflozin, have all shown to reduce the risk of HF-related hospitalization in persons with diabetes and at least stage 3a CKD [175–177]. Until more data are available, caution must be exercised with their use in CKD stage 4. Digoxin should be used with extreme caution in dialysis patients given the potential for serious side effects. Furthermore, observational data have suggested increased mortality with the use of digoxin in this population, although admittedly these studies may be limited by indication bias [178].

Conclusion

Persons with CKD, including those treated with dialysis, have a significant burden of CVD. Aggressive risk factor modification and treatment of CVD should be considered in the care of this population, particularly those with nondialysis CKD, keeping in mind these individuals are also at a higher risk of adverse outcomes from the interventions themselves, stressing the role of individualized care. Further clinical studies of CVD should focus on and include patients with advanced kidney disease.

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CHAPTER

15

Effects of nutritional status and changes in nutrient intake on renal function

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Introduction

Nutritional management and dietary intake have a major impact on kidney health and longevity. Among the macronutrients a large body of evidence has shown that increased dietary protein engenders changes in renal hemodynamics, kidney function, and kidney morphology. It has also been shown that various individual amino acids may have differential effects on kidney function, according to their site of metabolism. There has also been growing interest in the impact of dietary protein sources on kidney health outcomes, with more salutary benefits observed with plant-based, low-fat dairy, and white meat sources as opposed to red meat sources. Multiple concurrent mechanisms may mediate the protein- and amino acid–induced changes in kidney function and morphology, including endocrine factors [e.g., growth hormone (GH), insulin-like growth factor-1 (IGF-1), glucagon, renin–angiotensin–aldosterone, dopamine, atrial peptides] or local mediators [e.g., eicosanoids, nitric oxide (NO)]. To date, the direct impact of dietary carbohydrate and fat intake on kidney function and structure has not been well studied, but emerging evidence suggests potential associations between the dietary intake of these macronutrients, including amount and type, with the development and progression of chronic kidney disease (CKD). In the nonkidney disease population, certain dietary patterns [e.g., Dietary Approaches to Stop Hypertension (DASH), Mediterranean diets] have been endorsed by clinical practice guidelines given their favorable effects on hypertension, diabetes, cardiovascular risk, and survival and long-term sustainability. As examination of dietary patterns provides a more comprehensive and synergistic assessment of nutritional status in lieu of single nutrients, an increasing number of studies have also examined the impact of the DASH and Mediterranean diets on the development and progression of CKD.

Distinction should be made between intentional versus unintentional modulation of dietary intake, as these two entities have differential effects on kidney health outcomes. While prescribed low-protein diets in nourished adults have been shown to ameliorate CKD progression, unintentional reductions in dietary protein intake due to protein-energy wasting may lead to acute physiologic changes in renal hemodynamic, kidney function, urinary concentration, and sodium handling. Furthermore, early exposure to malnutrition may have long-term adverse sequelae, and growing research has shown that maternal malnutrition and isocaloric dietary protein restriction even in the pre- and peri-conception periods as well as over the course of pregnancy have an important bearing on kidney growth and/or function in later life.

In this chapter, we review the current evidence regarding (1) the effects of dietary protein and amino acids, other macronutrients (e.g., carbohydrate, fat), and dietary patterns on CKD outcomes; (2) pathways mediating the effects of macronutrient intake on kidney parameters; (3) the impact of protein energy–wasting malnutrition on kidney health outcomes; and (4) the impact of maternal nutritional status on the development and progression of CKD.

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Impact of nutritional status on kidney function

Dietary protein intake on kidney function and structure

A large body of evidence has shown that dietary protein and/or amino acid intake leads to changes in renal hemodynamics, kidney function, and kidney morphology (Fig. 15.1). In 1906, one of the first reports of the effects of dietary protein intake on kidney status showed that rats that were fed higher-than-usual amounts of dietary protein intake developed *increased kidney weight* over time [1]. Subsequent studies in both animals [2–8] and humans [9] have also shown that higher protein and/or amino acid loads result in *increased kidney size*.

Numerous studies have also shown that protein and/or amino acid ingestion also leads to *functional changes of the kidney*, including *increased renal blood flow* and *glomerular filtration rate* (GFR) in animals [10–13] and humans [14–19]. For example, in a study of 37 healthy adults who were administered mild, moderate, and large protein meals (defined as 0.55, 1.08, and 1.35 g/kg, respectively), there was a positive dose-dependent relationship between the amount of oral protein intake and GFR ascertained by inulin clearance and renal blood flow defined by *p*-aminohippurate clearance [20]. Similarly, in a study of eight healthy adults who underwent intravenous administration of balanced amino acids solution at varying dates, increasingly higher infusion rates were associated with a dose-related rise in GFR and renal blood flow [21]. In another study of eight healthy adults who were given a low- and high-protein diet for 6 days each, GFRs were observed to be higher on the high-protein diet and acutely rose within 1 hour and peaked at 2 hours following the protein load [22].

In diabetic patients, it has also been suggested that high protein intake may be more detrimental to patients with diabetes than those without diabetes. In a study of 12 diabetic patients versus 9 controls who underwent an overnight fast followed by an amino acid infusion, a more exaggerated increase in GFR and renal plasma flow with amino acid infusion was observed in the diabetic versus nondiabetic patients [23]. Conversely, it has been suggested that high-protein parenteral and/or enteral nutrition should be considered during an acute kidney injury (AKI) event to promote glomerular perfusion and faster recovery of the nephron (i.e., increased circulating amino acid levels in the blood dilate afferent arterioles of the glomeruli and increase renal perfusion and intraglomerular pressure) and to provide adequate nutritional support particularly during critical illness, such that a CKD patient on a low-protein diet should be temporarily transitioned to high-protein diet during the AKI period [24].

The onset of protein-induced alterations in renal hemodynamics that occur immediately after a protein and/or amino acid load may persist in the short term; however, the long-term effects of high protein loads on kidney health are less clear. Continuous *short-term intake* (i.e., days to weeks) of a high-protein diet appears to have similar effects on renal hemodynamics as that of acute postprandial kidney responses to high protein loads [22,25], although some studies [26–28] have not observed changes in GFR or renal blood flow. In healthy adults, it has also been suggested that variations in age [27], activity level, and/or nutritional status may result in differential effects of short-term high dietary protein loads on kidney function [29]. With respect to *long-term effects*, randomized trials [30,31], observational studies, and meta analyses [32–36] have suggested that high dietary protein intake may lead to

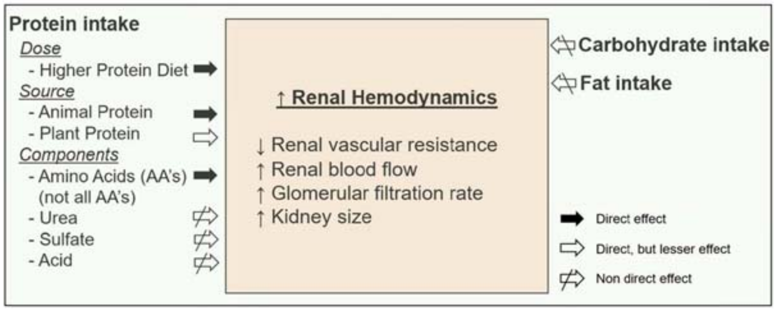

FIGURE 15.1 Impact of changes in macronutrient and amino acid intake on renal hemodynamics. Among the macronutrients, dietary protein intake directly affects postprandial renal hemodynamics. There is a dose-dependent increase in renal hemodynamics after protein intake. Varying sources of dietary protein may have differential effects on kidney function: animal protein, especially red meat intake, may stimulate renal hemodynamics, whereas plant protein has a lesser effect. As components of protein, amino acids may directly affect renal hemodynamics, whereas peripherally metabolized amino acids, such as branched-chain amino acids, may have no relationship to renal hemodynamics. Carbohydrate and fat intake may have indirect effects on kidney function (i.e., hyperglycemia, metabolic syndrome, obesity), but further research in this area is needed.

increased glomerular hyperfiltration and subsequent kidney dysfunction [29,35,37]. Yet in the scientific and lay communities, the long-term impact of high dietary protein intake on the risk of CKD and end-stage renal disease (ESRD) remains unclear, while more recent data and discussions imply that high protein intake may cause harm to kidney health in the long term [35,38,39].

Protein sources, amino acids, and kidney function

Growing evidence suggests that varying sources of dietary protein intake have disparate effects on kidney function and health [40–42]. While dietary protein from red meat sources has been associated with adverse effects on kidney function, dietary protein from plants, dairy products, and white meat may have a protective effect on kidney health. However, further research is needed to determine the impact of specific dietary protein sources on short- and long-term kidney functions.

The ingestion of various individual amino acids may also have differential effects on kidney function (Table 15.1), according to their site of metabolism [43–45]. Most amino acids are metabolized in the liver, whereas branched-chain amino acids (BCAAs) (e.g., valine, leucine, isoleucine) are catabolized in peripheral organs, particularly in skeletal muscle. Hence, while the group of amino acids that are preferentially metabolized in the splanchnic region contribute to alterations in postprandial renal hemodynamics, amino acids that are peripherally metabolized such as BCAAs do not appear to lead to glomerular hyperdynamic stimulation [46]. Indeed, several studies suggest that supplemented BCAAs may have beneficial effects on kidney health, including slowed progression of kidney disease due to diminished glomerular hyperdynamic stimulation [47,48]. These less stimulatory effects on renal hemodynamics by BCAAs versus other amino acids may be explained by the metabolic features of BCAAs. Indeed, humans with excess intake of BCAAs may have postprandial adaptations in which they do not experience change in renal hemodynamics. BCAAs taken in excess of their requirements are catabolized via reversible transamination to the branched-chain α-keto acids (BCKAs), followed by irreversible oxidative decarboxylation of BCKAs by the dehydrogenase enzyme complex (BCKD) [49]. The importance of efficient BCAA catabolism may be in part due to the fact that excess BCAAs or BCKAs due to inborn errors of BCAA metabolism are toxic to the central nervous system [49]. However, BCKD distribution is not consistent across organs, and the kidney shows relatively low capacity for BCKD compared to other organs, including muscle [50,51]. Indeed, it has been confirmed that there is no significant renal uptake of BCAAs in the postabsorptive phase [52]. In normal subjects, kidneys excrete mostly glutamine (58% of total amino acid excretion) as well as proline, citrulline, and phenylalanine, while it releases serine (37% of total amino acid output), plus taurine, threonine, tyrosine, ornithine, lysine, and arginine into the circulation. Interestingly, chronically insufficient kidneys are also not responsible

TABLE 15.1 The effects of individual amino acids and/or amino acid categories on renal hemodynamics across studies.

Amino acid(s)	Human subjects[a]	Dogs[b]	Rats
Glucogenic amino acids			
Arginine	GFR↑, RPF↑		GFR↑, RPF↑
Glycine	GFR↑, RPF↑	GFR↑ (given intravenously)	
Proline	GFR↑, RPF↑	GFR↑	
Cysteine	GFR↑, RPF↑	GFR→	
Methionine	GFR↑, RPF↑		
Serine	GFR↑, RPF↑	GFR→	
Alanine	Renal hemodynamics→	GFR↑	
BCAA	Renal hemodynamics→		
Threonine		GFR↑	
Glutamic acid		GFR↑	
Aspartic acid		GFR↑	
Valine		GFR↑	

[a] *Administered intravenously.*
[b] *Administered via stomach tube.*
↑, Increase; →, not changed. *BCAA*, Branched-chain amino acid; *GFR*, glomerular filtration rate; *RPF*, renal plasma flow.

for BCAA excretion [52]. Furthermore, BCAAs (particularly leucine) not only function as a protein substrate but also as an anabolic substance promoting stimulation of protein synthesis in skeletal muscle, liver, and adipose tissues [53] and inhibition of protein breakdown [54].

Pathways mediating the impact of dietary protein and amino acid intake on kidney health

The mechanisms underlying protein- and amino acid–induced changes in kidney function and morphology may be related to endocrine or local mediators, as well as intrarenal mechanisms as described in Table 15.2.

Humoral mediators

Growth hormone and insulin-like growth factor-1 axis

GH and IGF-1 have been implicated as major hormonal mediators in the renal response to protein loads, including alterations in kidney size and structure and increased renal blood flow and GFR. Most of GH's effects are mediated by growth factors induced by GH in target organs and tissues such as the kidney, as well as the liver, adipose tissue, heart, and skeletal muscle [55]. Among these, IGF-1 is the most physiologically relevant and most extensively studied GH-induced growth factor [56].

GH and IGF-1 levels rise following protein and/or amino acid ingestion [17,57,58], and GH and IGF-1 both directly impact kidney structure, as well as glomerular and tubular function. For example, mice with greater representation of GH genes demonstrate renal hypertrophy, manifested as increased kidney size and weight, glomerular hypertrophy, mesangial proliferation, and glomerulosclerosis [59,60]. In studies of patients with acromegaly, limited data have shown evidence of glomerular hypertrophy [61], whereas other studies have shown marked increases in GFR and renal plasma flow following GH and IGF-1-mediated reductions in renal vascular resistance [62–64]. In addition, acromegalic states are associated with increases in total body water and sodium retention and subsequent

TABLE 15.2 Pathways mediating the impact of dietary protein and amino acid intake on kidney status.

Mediator category	Factor	Mechanism	Effects on kidney status
Endocrine	Growth hormone/insulin-like growth factor-1 axis	Disproportionate renal growth	Renal hypertrophy (increased kidney size/weight, glomerular hypertrophy, mesangial proliferation, glomerulosclerosis)
		↓Renal vascular resistance	Changes in glomerular function (↑renal blood flow, ↑GFR)
		Soft-tissue enlargement, ↑ENaC-dependent sodium transport	Body fluid retention (sodium and water expansion, ↑sodium reabsorption)
		↑Calcitriol → ↑Ca absorption, ↑tubular Ca reabsorption	Changes in calcium–phosphorus metabolism (mild hyperphosphatemia, hypercalcemia, hypercalciuria)
	Glucagon	↑cAMP	Changes in glomerular function (↑renal blood flow, ↑GFR). ↓Tubular urea reabsorption
	Renin–angiotensin–aldosterone system	↑Renin mRNA	↑PRA
	Dopamine	Via D_1–like receptors	Renal hemodynamics (↑renal blood flow, ↓renal vascular resistance)
		Via D_2–like receptors (especially D_3R_s)	Renal hemodynamics (↑GFR)
		Via D_1–like receptors and D_2-like receptors	↑Ion and water excretion (during salt-replete states)
	Atrial peptide		↑Vasodilation → ↓GFR
Local	Eicosanoids	↑PE-PLA_2 → ↑eicosanoids (PGE_2, $PGF_{2\alpha}$, 6-keto $PGF_{1\alpha}$) and ↑COX activity	↑Renal blood flow, ↑GFR
	Nitric oxide	↑NOS availability	↑Renal blood flow, ↑GFR

6-keto $PGF_{1\alpha}$, 6-Keto prostaglandin $F_{1\alpha}$; *cAMP*, cyclic adenosine monophosphate; *COX*, cyclooxygenase; *GFR*, glomerular filtration rate; *mRNA*, messenger RNA; *NOS*, nitric oxide synthase; *PE-PLA_2*, phosphatidylethanolamine-specific phospholipase A2; *PGE_2*, prostaglandin E_2; *$PGF_{2\alpha}$*, prostaglandin $F_{2\alpha}$; *PRA*, plasma renin activity levels.

soft-tissue enlargement [65,66], independent of effects by the renin–angiotensin–aldosterone system or atrial natriuretic peptides (ANP) [67]. Patients with acromegaly have also shown alterations in mineral bone disease metabolism, including mild hyperphosphatemia, heightened intestinal calcium absorption, and increased tubular calcium reabsorption [68,69], which may potentially have ill effects on kidney function and structure. Notably, mice transgenic for IGF-1 do not develop glomerulosclerosis and have less severe glomerular hypertrophy [59,70]. Thus it is conceivable that GH or GH-induced increased IGF-1 levels, with the existence of functional GH or IGF-1 receptors, might be a mediator of the renal response to protein and amino acids.

However, it bears mention that the role of GH and IGF-1 in the renal response to protein and/or amino acid intake has been questioned in some studies showing that protein-related increases in renal plasma flow and GFR occurred prior to or in the absence of increased GH levels. Furthermore, GH-deficient patients have also exhibited renal vasodilation following amino acid infusion [22,71,72]. Hence, further research is needed to clarify the contribution of GH and IGF-1 to dietary protein-related alterations in kidney structure and function.

Glucagon

Glucagon is not only a glucose regulatory hormone but is also considered a key player in amino acid metabolism and nitrogen excretion following dietary protein intake or amino acid administration. After a dietary protein load or an amino acid infusion, there is an increase in glucagon secretion [73–75]. Concurrent with the rise in plasma glucagon levels, there is a dose-dependent increase in GFR that correlates with glucagon concentrations [17].

While the role of glucagon has been strongly suspected as a mediator of glomerular hyperfiltration, other studies have shown contrary findings. For example, some studies have not observed significant correlations between plasma glucagon concentrations and the rise in GFR [76]. Other research have also shown that GFR changes following an amino acid infusion were not correlated with glucagon in and of itself but were instead correlated with the glucagon-to-insulin ratio [77]. Some studies examining the mechanisms of glucagon-induced increases in GFR have also revealed that there are simultaneous rises in plasma glucagon and cyclic adenosine monophosphate (cAMP) levels that are required for glomerular hyperfiltration. These glucagon-induced changes in GFR were significantly and positively correlated with simultaneous changes in plasma cAMP levels, largely derived from the liver, and in the urine-to-plasma urea level ratio [78]. Other studies have found that increased peripheral blood glucagon levels after protein meal ingestion did not result in higher GFRs [79,80], and infusion of glucagon without coinfused cAMP nor cAMP alone were not associated with increases in GFR [79]. These latter observations suggest that the simultaneous effects of dietary protein-induced increases in plasma glucagon and extracellular cAMP are responsible for rises in GFR following a protein or amino acid load.

Renin–angiotensin–aldosterone system

It is well established that dietary protein regulates both the synthesis and release of renin [81–85], as well as renin–angiotensin–aldosterone activity in modulating glomerular hemodynamics [86]. Renin may have greater implications as a mediator of the long-term effects of protein consumption on kidney health, as opposed to the acute renal response to protein intake. Indeed, most studies indicate that plasma renin activity and angiotensin II levels do not acutely rise during protein ingestion [72,87,88]. In contrast, studies have shown that subacute and chronic alterations in dietary protein intake modulate plasma renin activity. For example, a study in seven healthy adults showed plasma renin activity levels were significantly higher after 5 days of high dietary protein intake (i.e., 2.0 g/kg/day) [89]. These observations have been corroborated in other studies of normal rats [82,83], healthy adults [90], and in patients with kidney failure [91]. In terms of the latter, experimental animal models examining changes in renal messenger RNA (mRNA) levels suggest that high protein loads contribute to increased plasma renin activity. Normal rats that were fed a high-protein diet (i.e., comprising 50% protein) demonstrated greater increases in renin mRNA levels in comparison to rats fed a standard protein diet (i.e., comprising 24% protein) [84]. Similarly, in a study of subtotal nephrectomized rats, renal renin mRNA levels were higher in the high-protein diet group (i.e., comprising 40% protein, administered for 7 days following 7 days of low-protein diet intake) compared to those in the low-protein diet group (i.e., comprising 6% protein, administered for 14 days) [81].

Dopamine

The kidneys synthesize dopamine from circulating or filtered decarboxylated L-3,4-dihydroxyphenylalanine (L-DOPA), the major source of renal dopamine production [92], independent of renal innervation. Although sodium intake and intracellular sodium are thought to be the major determinants of the renal tubular synthesis/release of dopamine [93,94] a high protein load [95,96] or feeding [97] may increase urinary dopamine levels, which may be secondary to an increase in L-DOPA synthesis.

Increased levels of dopamine act on the kidney via two families of cell-surface receptors, D_1- and D_2-like receptors. Dopamine largely acts via D_1-like receptors to augment renal vasodilation, renal blood flow [98–100], and urinary volume and ion excretion, including natriuresis [101,102]. In contrast, the effects via D_2-like receptors are dependent upon the state of nerve activity and may be associated with an increase in GFR [103,104]. An acute increase in the amount of protein ingested with a single meal or a chronic increase in dietary protein intake over several days raises brain tyrosine levels and stimulates catecholamine synthesis, including dopamine [105]. Thus protein and/or amino acid loads have effects on kidney function via both intrarenal dopamine and innervation-related dopamine pathways.

Atrial peptides

Previous studies examining ANP as a potential mediator of the renal response to protein ingestion have shown mixed findings. It is well known that ANP increases GFR by promoting direct vasodilatory effects on the afferent arterioles, thereby allowing more blood to enter the glomerulus for ultrafiltration [106,107]. However, there are sparse data supporting a role for ANP in protein-related increases in GFR. Some research have shown that plasma ANP levels were elevated following a high-protein meal (i.e., 1.0–1.5 g of protein/kg) [108], while other studies have demonstrated that plasma ANP levels were elevated only after the first hour after a high-protein meal ingestion (i.e., 10.0 g of lean beef/kg) [109] or were in fact decreased or remained unchanged after high-protein consumption (i.e., 1.0 g of protein/kg) [110,111]. Furthermore, among these studies, it was found that plasma ANP levels were not significantly associated with creatinine clearance after a protein meal [109].

Local mediators

Eicosanoids

In animal models, protein-induced augmentation of GFR and renal blood flow are accompanied by increases in glomerular production of eicosanoids [83,112,113]. Eicosanoids are locally acting bioactive signaling lipids that regulate a broad range of homeostatic and inflammatory biologic processes [114,115]. Synthesis of these local mediators occurs through enzymatic or nonenzymatic free radical mechanisms following the oxidation of arachidonic acid [116]. As the first step of eicosanoid biosynthesis, phospholipase, including phosphatidylethanolamine-specific phospholipase A2 ($PE\text{-}PLA_2$), phosphatidylcholine-specific phospholipase A2, and phosphatidylinositol-4,5-biphospate-specific phospholipase C play an important role in increasing the levels of free arachidonic acid from its esterified stored form. Eicosanoids are then derived from free arachidonic acid thorough one of three pathways, cyclooxygenase (COX), lipoxygenase, and cytochrome P450 pathways, or via nonenzymatic free radical mechanisms.

Some studies have demonstrated the subacute and chronic effects of a high-protein diet (i.e., 2 weeks [117] or 6 weeks [118]) on glomerular eicosanoid production in normal rats as well as rats with glomerular disease. These data have demonstrated the modulating effect of dietary protein on glomerular eicosanoid production, specifically stimulation of glomerular synthesis of prostaglandin E_2, prostaglandin $F_{2\alpha}$, and 6-keto prostaglandin $F_{1\alpha}$, eicosanoids generated via the COX pathway, in both normal and glomerular diseased rats. This dietary protein-induced modulation of glomerular eicosanoid production was also observed irrespective of the presence or absence of arachidonic acid, indicating that dietary protein augmented glomerular COX activity. Another study examining intraglomerular mechanisms underlying dietary protein-induced production of eicosanoids showed that this may be mediated by augmentation of COX levels and activity, coupled with enhanced activity of $PE\text{-}PLA_2$ [118].

Nitric oxide

NO is a well-known vasodilator produced by the vascular endothelium via the enzyme endothelial NO synthase (eNOS). Dietary protein and amino acid intake and other dietary factors are known to modulate NO production [119–121]. Low dietary protein intake results in reduced NO production via decreased expression of the enzymes and essential cofactors needed for its synthesis [122]. For example, L-arginine and citrulline are substrates for eNOS in the synthesis of NO in almost all mammalian cells [123–125]. Furthermore, citrulline is a precursor of L-arginine and is converted from L-citrulline to L-arginine by the kidneys in the production of NO [126,127]. In turn, NO is involved in numerous physiologic processes that impact both acute and chronic regulation of kidney function and systemic blood pressure [128–135]. With respect to renal hemodynamics, in animal models, the inhibition of NO synthesis (i.e., via administration of structural analogs of L-arginine) was shown to prevent or blunt the effects of amino acid stimulation of renal vasodilation, increased renal blood flow, and increased GFR [136–140].

Dietary carbohydrate intake and kidney function

The direct impact of dietary carbohydrate on kidney function has not been well studied, although emerging evidence suggest a potential association with the development of CKD [141,142]. Indeed, a growing number of experimental animal models and epidemiologic studies have examined the short- and long-term implications of amount of dietary carbohydrate intake and/or dietary carbohydrate type on kidney function, which have shown mixed findings (Table 15.3).

In one experimental study of dogs, dietary carbohydrate and fat intake were not associated with acute (i.e., postprandial) nor subacute (i.e., weekly) alterations in renal hemodynamics [143]. Yet findings from a randomized trial of 163 overweight/obese adults without underlying diabetes or kidney disease suggest that dietary carbohydrate type and amount may have short-term implications on kidney function [144]. In this study, participants were administered four types of diets, combinations of high versus low glycemic index diets and high versus low carbohydrate diets (defined by proportion of total energy intake) over a 5-week period, and concurrent receipt of low glycemic index and low carbohydrate diets had additive effects on increasing GFR while maintaining constant body weights. These data signal the potential short-term benefits of low glycemic index diets (i.e., comprising complex carbohydrates, fiber, and other beneficial nutrients) upon kidney health. With respect to the carbohydrate amount, it is possible that the short-term rise in GFR observed with lower carbohydrate consumption may have been due to the substitution of dietary protein for dietary carbohydrate in the prescribed diets.

Limited studies that have examined the long-term impact of carbohydrate type and amount upon the development of incident CKD have also shown conflicting findings. In one observational study, 2600 healthy adults underwent assessment of dietary glycemic index ascertained by food frequency questionnaires and were followed for up to 5 years [145]. While cross-sectional analyses showed that the highest quartile of dietary glycemic index intake was associated with higher prevalence of moderate CKD [defined as an estimated GFR (eGFR) < 60 mL/min/1.73 m^2], longitudinal data did not support an association with incidence of kidney disease. In a more recent epidemiologic study of the Korean Genome Epidemiology Study, those in the highest two quartiles of dietary carbohydrate density intake (i.e., proportion of total energy take) ascertained by 24-hour dietary recall had a higher risk of developing CKD (defined as the composite of an eGFR ≤ 60 mL/min/1.73 m^2 and development of proteinuria) compared to those in the lower quartiles of intake [146]. Potential explanatory mechanisms of the relationship between higher dietary carbohydrate intake and CKD include the development of metabolic abnormalities (i.e., higher waist-to-hip ratios and HOMA-IR), inflammation, oxidative stress, and alterations in gut microbiota. Future studies are needed to determine the longitudinal impact of dietary carbohydrate intake amount and type upon kidney health, as well as the precise mechanisms underlying the link between dietary carbohydrate intake and kidney function.

TABLE 15.3 Selected studies of dietary carbohydrate intake (upper panel) and dietary fat intake (lower panel) and kidney function.

Reference	Population (*N*)	Exposure	Outcome
Carbohydrate			
Juraschek et al. [144]	Overweight/obese adults without diabetes or kidney disease (163)	Crossover intake of four diets: (1) high GI (≥65) with high % carb (58% kcal), (2) low GI (≤45) with low % carb (40% kcal), (3) low GI with high % carb, and (4) high GI with low % carb	Cystatin C, β2-microglobulin, and eGFR
Gopinath et al. [145]	Healthy adults (2600)	Quartiles of mean dietary GI intake ascertained by FFQ	Prevalence and 5-year incidence of moderate CKD
Nam et al. [146]	Adults without diabetes (6746)	Quartiles of dietary carbohydrate density (% energy) assessed by a 24-h dietary recall and FFQ	Incidence of moderate CKD and development of proteinuria
Fat			
Lin et al. [154]	Nurses' Health Study (3348 with albuminuria, 3296 with eGFR change)	Quartiles of energy-adjusted dietary intake, including saturated fat and animal fat ascertained by FFQ	Presence of microalbuminuria and incidence of eGFR decline ≥30%
Lin et al. [155]	Reasons for Geographic and Racial Differences in Stroke cohort (19,256)	Daily dietary intake of total, saturated, monounsaturated, polyunsaturated, and trans-fat calculated from FFQ	Presence of high albuminuria or eGFR < 60 mL/min/1.73 m^2
Foster et al. [153]	Framingham Heart Study (2923)	Renal sinus fat defined using sex-specific 90th percentiles in a healthy reference subsample	Presence of eGFR < 60 mL/min/1.73 m^2

CKD, Chronic kidney disease; *eGFR*, estimated glomerular filtration rate; *FFQ*, food frequency questionnaire; *GI*, glycemic index.

Dietary fat intake and kidney function

There has been growing interest in the impact of dietary fat intake on metabolic health and downstream kidney disease. Several studies in animals and humans have supported long-term associations between higher dietary fat intake and alterations in kidney structure and function (Table 15.3). It has been hypothesized that prolonged metabolic perturbations (i.e., persistent hyperglycemia, obesity, inflammation) induced by a high-fat diet may contribute to kidney damage over time.

Experimental animal models have shown that long-term intake of high-fat diets over an 8- to 12-week period leads to renal fat accumulation with concomitant changes in kidney structure and function. In these studies the amount of dietary fat ranged from 15% [147] to 30% [148] to 60% [149] of total energy intake and was derived from saturated fat sources, including lard, beef tallow, and coconut oil. Different types of dietary fat have been noted to have varying effects on kidney health. For example, in a study of spontaneously hypertensive rats that were fed five different types of edible oils (e.g., fish, canola, palm, olive, and soybean) versus placebo for 13 weeks, rises in blood pressure as well as glomerulosclerosis, glomerular enlargement, and glomeruli loss were prevented among those that received fish, canola, and palm oils and were attenuated in those that received olive and soybean oils [150]. Notably, the most favorable effects were observed with fish oil administration (source of $n-3$ polyunsaturated fatty acids, eicosapentaenoic and docosahexaenoic acids), followed by canola and palm oils, and finally olive and soybean oils. In another study of rats that were administered four types of high-fat diets (e.g., soybean oil, canola oil, lard + egg yolk, and canola oil + lard + egg yolk), those that were fed soybean or canola oil had greater preservation of glomerular size and number [151]. Finally, in a study of rats across varying ages that were fed 5%-lipid-enriched diets with three different sources of fat (e.g., canola oil, fish oil, and butter) versus a control diet, those that were fed any of the lipid-enriched diets had faster onset of increased proteinuria than controls [152]. While age-related decline in GFR and renal blood flow were observed in all lipid-enriched diet groups, deterioration in these parameters was most marked in those receiving butter and fish oil.

Epidemiologic studies have also signaled a relationship between higher dietary fat intake and CKD [153]. In a study of 3348 women from the Nurses' Health Study, greater intake of animal fat was significantly associated with higher risk of albuminuria [154]. In addition, higher intake of total fat, saturated fat, and animal fat was each associated with higher risk of eGFR decline. Similarly, in a study of 19,246 men and women from the Reasons for Geographic and Racial Differences in Stroke cohort, greater intake of saturated fat was associated with higher risk of albuminuria [155]. However, in this study, total fat nor other types of dietary fat were not associated with risk of albuminuria or eGFR decline.

With respect to the short-term implications of dietary fat, limited research to date has not identified an association between higher fat consumption and adverse CKD outcomes [156]. In an experimental study of Sprague Dawley rats that were fed high-fat and/or high-sugar diets (e.g., excess lard, sucrose, or a combination of lard + sucrose) over a 4- and 8-week period, while there was a significant increase in weight and abdominal fat over these time periods, while no changes in kidney mass were observed [156]. In another study of Sprague Dawley rats that were fed a high-fat diet versus standard chow over a 6-week period, while the high-fat diet was found to increase adiposity and renal mass, there was no evidence of early kidney injury ascertained by urinary and plasma biomarkers (urine to protein creatinine ratio, plasma cystatin C) nor renal histology. These limited observations suggest that short-term metabolic changes (i.e., moderate hyperglycemia, inflammation) induced by a high-fat diet are not sufficient to cause kidney damage, nor does a ketogenic, high-fat diet contribute protection to the kidney [157]. Similarly, dietary fat and dietary carbohydrates have not been observed to cause acute or short-term (i.e., postprandial or over weeks) changes in renal hemodynamics [143].

Dietary types and kidney function

While renal nutrition has historically focused on single nutrients (i.e., macronutrients, micronutrients, or other bioactive substances present in food), there has been growing interest in studying dietary patterns (i.e., comprehensive examination of nutrients, foods, food groups, combinations, as well as their variety, frequency, and quantity in habitual diets) that may be more predictive of overall kidney health status and CKD risk (Table 15.4) [158,159]. Indeed, using a "food synergy" approach/strategy, which is based on the assumption that in most cases food substances have additive or synergistic effects on health, may provide more meaningful and pragmatic guidance to patients and the public health community in promoting sustainable dietary behaviors that promote kidney health.

Dietary Approaches to Stop Hypertension diet

The DASH diet is a dietary pattern that has been endorsed by the US National Institutes of Health for

TABLE 15.4 Selected studies of dietary types and kidney function.

Reference	Population (*N*)	Exposure	Outcome
DASH diet			
Lin et al. [33]	Nurses' Health Study (3121)	Quartile of three dietary pattern scores: (1) prudent, (2) Western, and (3) DASH style dietary patterns ascertained by FFQ	Presence of microalbuminuria, incidence of eGFR decline $\geq 30\%$, and rapid eGFR decline ($\downarrow$eGFR ≥ 3 mL/min/1.73 m^2/year)
Crews et al. [167]	Urban adults with poverty versus nonpoverty status (2058)	Tertiles of DASH ascertained by FFQ	Incidence of CKD
Rebholz et al. [169]	ARIC study (14,882)	Tertiles of DASH score ascertained by FFQ	Incidence of CKD, kidney disease−related hospitalization or death, or end-stage renal disease
Asghari et al. [168]	Tehran Lipid and Glucose Study (1630)	Quintiles of DASH score ascertained by FFQ	Incidence of CKD
Mediterranean diet			
Chrysohoou et al. [175]	Men and women (3042)	Adherence to the Mediterranean diet assessed a validated diet score (MedDiet Score)	Creatinine clearance rate
Mazaraki et al. [174]	Leontio Lyceum ALbuminuria (3L) Study (365)	Three categories of Mediterranean Diet Quality Index: high, average, and low scores	Prevalence of microalbuminuria
Díaz-López et al. [173]	PREDIMED study (785 in cross-sectional analyses and 665 in longitudinal analyses)	RCT with three arms: (1) Mediterranean diet supplemented with virgin olive oil, (2) Mediterranean diet supplemented with mixed nuts, or (3) low-fat control diet	BUN, serum creatinine, albuminuria, and eGFR
Khatri et al. [176]	NOMAS (900)	Mediterranean diet score dichotomized as the median ascertained by FFQ	Incidence of CKD or upper quartile of annualized eGFR decline ($\downarrow \geq 2.5$ mL/min/1.73 m^2/year)
Asghari et al. [177]	Tehran Lipid and Glucose Study (1212)	Quartiles of Mediterranean diet ascertained by FFQ	Incidence of CKD

ARIC, Atherosclerosis Risk in Communities; *BUN*, blood urea nitrogen; *CKD*, chronic kidney disease; *DASH*, Dietary Approaches to Stop Hypertension; *eGFR*, estimated glomerular filtration rate; *FFQ*, food frequency questionnaire; *NOMAS*, Northern Manhattan Study; *PREDIMED*, Prevención con Dieta Mediterránea; *RCT*, randomized controlled trial.

the prevention and management of hypertension. The DASH diet is rich in fruits, vegetables, whole grains, and low-fat dairy products but notably is not a low-protein diet; it also includes fish, poultry, beans, and nuts, whereas sugar-sweetened foods, red meat, and fats are limited [160]. The DASH diet has been recommended by multiple clinical practice guidelines for disease prevention and health promotion given its favorable impact on not only hypertension [161,162], but also type 2 diabetes [163,164], cardiovascular disease and stroke [165], and survival [166].

Large population-based studies have demonstrated that greater adherence to the DASH diet is associated with favorable renal outcomes. Greater adherence to the DASH diet has been associated with lower risk of incident CKD and/or CKD progression in the Nurses' Health Study [33]; participants from the Healthy Aging in Neighborhoods of Diversity across the Life Span cohort at the poverty level [167]; the Tehran Lipid and Glucose Study [168]; and the Atherosclerosis Risk in Communities cohort [169]. The individual components of the DASH diet, including its sources of protein (e.g., plant-based foods, low-fat dairy) and accompanying nutrients, may be the drivers of better kidney health trajectory [42]. Potential mechanisms by which greater adherence to the DASH diet may reduce incident CKD and CKD progression include reductions in blood pressure, attenuation of dietary acid load, and improvement in endothelial function [169].

Mediterranean diet

Similar to the DASH diet, the Mediterranean diet is balanced, flexible, has long-term sustainability, and supports lifestyle changes (i.e., increased physical activity), and has been recommended as a beneficial and sustainable dietary pattern for CKD patients [170]. The Mediterranean diet's components include greater consumption of fruits, vegetables, olive oil, legumes, and cereals; moderate-to-high intake of fish; moderate intake of dairy and wine; and low intake of red meat [171].

A growing number of studies have examined the association between the Mediterranean diet [172] and kidney outcomes, which have shown mixed findings.

In a clinical trial of community-dwelling adults in Spain from the Prevención con Dieta Mediterránea study, participants randomized to a Mediterranean diet + additional virgin olive oil, Mediterranean diet + additional mixed nuts, and a low-fat control diet showed similar improvements in kidney function after 1 year [173]. Yet a number of observational studies have shown that greater adherence to the Mediterranean diet is associated with lower risk of incident CKD and/or kidney function decline among children in the KIDMED cohort [174]; participants in the ATTICA study [175]; and adults in the Northern Manhattan and Tehran Lipid and Glucose cohorts [176,177].

Impact of protein-energy wasting on kidney function

Protein-energy wasting is a widespread public health problem that contributes to the morbidity and mortality in populations in which it is prevalent [178]. The abovementioned evidence has shown that a low-protein diet due to intentional reduction in dietary protein intake has a favorable impact on kidney function trajectory. In contrast, unintentional reductions in dietary protein intake likely due to protein-energy wasting have been linked with unfavorable kidney health outcomes, including acute reductions in GFR and renal plasma flow (Table 15.5), urinary concentrating defects, and acid–base disturbances as described next (Table 15.6 and Fig. 15.2).

Protein-energy wasting and kidney function

Short-term reductions in dietary protein intake have been shown to decrease GFR and renal plasma flow in normal subjects. In a clinical study of healthy young women and men that compared the effects of low dietary protein intake (defined as 0.3 g of protein/kg) with moderate dietary protein intake (defined as 1.0 g of protein/kg/day) over a 2-week period in the same subjects [179], low dietary protein demonstrated a fall in GFR as measured by inulin clearance and *p*-aminohippurate clearance, as well as effective renal plasma flow. Notably, these two diets were isocaloric and were designed to maintain constant body weights.

Protracted reductions in protein and caloric intake may result in protein-energy wasting with downstream alterations in kidney function (Table 15.5). Studies in both developed and developing countries have shown that both adults and children with protein and calorie malnutrition experienced acute changes in renal function that were reversed with repletion [178]. For example, in a study of 32 children from Jamaica whose ages ranged from 7 to 21 months old, those with protein and calorie malnutrition demonstrated reductions in GFR and renal plasma flow; following repletion and refeeding with protein, improvements in GFR and renal plasma flow were observed [180]. In another study of 10 adults with protein-energy wasting admitted to a metabolic ward in Colombia, patients underwent assessment of kidney function before and after protein repletion. These patients demonstrated

TABLE 15.5 Glomerular filtration rate and renal plasma flow in malnourished subjects.

Investigator	Malnourished				Repleted or normal			
	N	**C_{IN} (mL/min)**	**C_{PAH} (mL/min)**	**FF**	***N***	**C_{IN} (mL/min)**	**C_{PAH} (mL/min)**	**FF**
Alleyne [180]	8 children	47.1	249.4	0.21	14 children	92.4	321.2	0.29
	7 children[a]	42.9	184.0	0.27				
Arroyave et al. [189]	9 children	13.7	–	–	9 children	33.9	–	–
					17 normal children	45.0		
Gordillo et al. [188]	10 children	23.0	108.4		25 normal children	64.0	294	0.23
Klahr [181]	10 adults	64.1	325.8	0.20	10 adults	88.3	381.1	0.24
McCance [185]	11 adults	119.4	–			–		
	11 adults	100.9	–			–		
Mollison [184]	2 adults[a]	53, 70	283, 194[b]			–		
	2 adults	124, 141	340, 710[b]			–		

[a] *Edema was preset in these subjects at the time of study. Mean value are given in mL/min. The data for adults are corrected for 1.73 m^2. The data of Arroyave and Gordillo are expressed per m^2. The data of Alleyave are corrected for height (m^3).*

[b] *Diodone clearance.*

CIN, Clearance of inulin (mL/min); *CPAH*, clearance of *p*-aminohippurate (mL/min); *FF*, filtration fraction; *N*, no. of subjects.

Source*: From Klahr S, Alleyave GAO. Effect of chronic protein-calorie malnutrition on the kidney. Kidney Int 1973;3:129–41, with permission.*

TABLE 15.6 Effect of chronic protein-energy wasting on renal function in adults.

	Factor	Protein-energy wasting	Repletion
Renal hemodynamics	GFR	↓	↑
	Renal plasma flow	↓	↑
	Kidney size	↓?	–
Basic laboratory	Creatinine	→	→
	BUN	→	↑
	Proteinuria	–	–
	Albuminuria	↑	–
Urine	Volume	↑	↓
	Concentration	↓	–
	Maximal urine osmolality	↓	↑
	Free-water reabsorption	↓	↑
	Dilution	→	–
	Minimal urine osmolality	→	–
	Free-water clearance	→	–
Acid–base balance	Steady state	→	–
	Acid load-state	↓	–
Body water	Sodium retention	↑	–
	Edema	↑→	–

BUN, Blood urea nitrogen; *GFR*, glomerular filtration rate.

marked reductions in both GFR and *p*-aminohippurate clearance, increased following protein repletion [181].

In a more recent study of 1572 South Koreans from the prospective KoreaN Cohort Study for Outcomes in Patients with CKD cohort, lower dietary protein intake was associated greater decline in kidney function over time [182]. These associations were attenuated to the null following adjustment for markers of protein-energy wasting, suggesting that malnutrition may have been on the causal pathway between lower dietary protein intake and kidney function decline in this cohort.

Protein-energy wasting and renal hemodynamics

In adult subjects, severe protein-energy wasting not only leads to decreased GFR but also reduced renal plasma flow [181,184–187]. As noted earlier, among the 10 adults with protein-energy wasting admitted to a metabolic ward in Colombia who demonstrated marked reductions in renal plasma, normalization of renal hemodynamics was observed following protein repletion [181]. In another study of four adults with malnutrition in a concentration camp of Belsen after World War II, reduced renal plasma flow was observed in subjects with malnutrition and edema, whereas normal renal plasma flow was observed in those with malnutrition but without edema [184]. However, in another study of 11 adults with "undernutrition" (i.e., lesser degree of malnutrition than the abovementioned studies), only 1 out of 11 subjects demonstrated renal plasma flow falling below 100 mL/min [185]. Studies of protein-energy wasting in children have more consistently demonstrated reductions in renal plasma flow and improvement following protein repletion [180,188,189]. Given that the renal hemodynamic alterations in the abovementioned studies were largely improved following dietary protein repletion, it is likely that these reductions in renal plasma flow reflect a physiologic adaptation to severe protein-energy wasting.

Possible mechanisms by which protein-energy wasting contributes to an acute decline in renal plasma flow and GFR have been theoretically well-defined, but the actual regulation of filtration remains less clear [181]. The driving force for GFR is the balance of hydrostatic and oncotic pressure across the glomerular membrane. Notably, varying durations and severity of protein-energy wasting may lead to differential

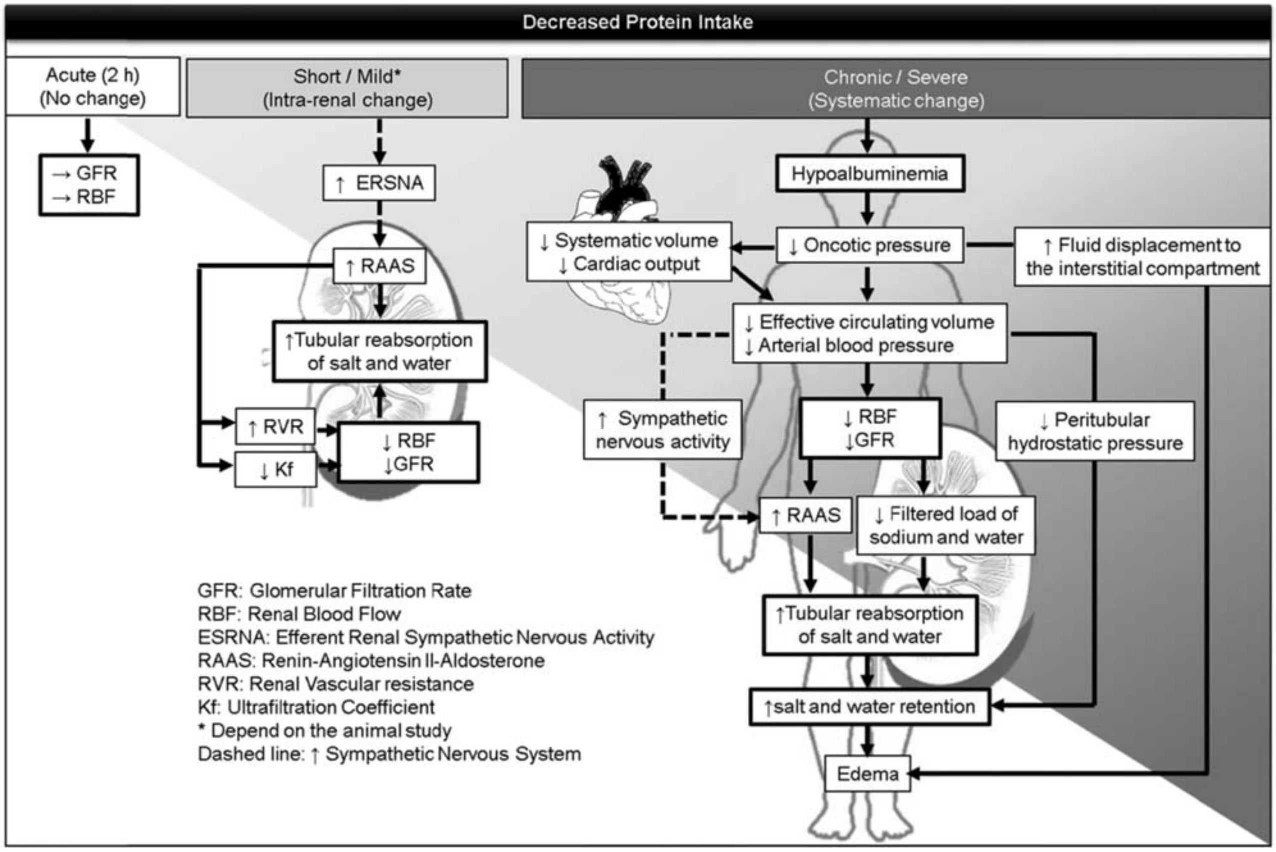
Decreased Protein Intake
Acute (2 h) (No change)
Short / Mild* (Intra-renal change)
Chronic / Severe (Systematic change)
→ GFR
→ RBF
↑ ERSNA
↑ RAAS
↑Tubular reabsorption of salt and water
↑ RVR
↓ Kf
↓ RBF ↓GFR
Hypoalbuminemia
↓ Systematic volume ↓ Cardiac output
↓ Oncotic pressure
↑ Fluid displacement to the interstitial compartment
↓ Effective circulating volume ↓ Arterial blood pressure
↑ Sympathetic nervous activity
↓ RBF ↓GFR
↓ Peritubular hydrostatic pressure
↑ RAAS
↓ Filtered load of sodium and water
↑Tubular reabsorption of salt and water
↑salt and water retention
Edema
GFR: Glomerular Filtration Rate
RBF: Renal Blood Flow
ESRNA: Efferent Renal Sympathetic Nervous Activity
RAAS: Renin-Angiotensin II-Aldosterone
RVR: Renal Vascular resistance
Kf: Ultrafiltration Coefficient
* Depend on the animal study
Dashed line: ↑ Sympathetic Nervous System

FIGURE 15.2 Impact of protein-energy wasting on glomerular filtration, renal hemodynamics, urinary concentration, and sodium excretion.

patterns of renal hemodynamic changes induced by a low-protein diet. During early stages or mild degrees of decreased dietary protein intake, systemic manifestations may be absent and reductions in renal blood flow, GFR, and tubular reabsorption of salt and water may depend on the activity of the efferent renal sympathetic nervous system, which influences renin secretion from the kidney [190,191]. With efferent renal sympathetic nerve activity stimulation, increases in angiotensin II–induced renal tubular sodium reabsorption, renal vasoconstriction, renal blood flow, and GFR are observed [191–193]. With prolonged and severe reductions in dietary protein intake, efferent renal sympathetic nerve activity and systematic changes impacting renal hemodynamics may occur. Indeed, in studies of both adults [194] and children [195] with protein-energy wasting, reductions in cardiac output have been reported. Ensuing reductions in systemic blood pressure and cardiac output may consequently lead to decreased glomerular hydrostatic pressure. However, concurrent reductions in circulating plasma protein levels would lead to decreased glomerular capillary oncotic pressure, thereby favoring glomerular filtration.

Protein-energy wasting and laboratory measures of kidney function (serum creatinine and urea nitrogen)

Higher levels of serum creatinine and blood urea nitrogen (BUN) are used as proxies of severe kidney disease (stage 5) among patients without protein-energy wasting. However, in patients with protein-energy wasting, serum creatinine and BUN levels have a tendency to be normal or low even in the context of moderately to severely impaired GFR [181]. Reasons for the lack of rise in serum creatinine and BUN levels in this setting include (1) reductions in muscle mass ensuing from chronic deprivation of protein intake and (2) decreased protein consumption leading to reduced tissue–protein breakdown and urea reutilization (Fig. 15.3) [196]. Among adults with protein-energy wasting, habitual reductions in dietary protein intake have been associated with marked decreases in GFR ascertained by creatinine and inulin clearance [181]. However, it should be noted that patients demonstrated normal or subnormal serum creatinine and BUN levels that were normal or below normal, likely due to masking of kidney dysfunction as a result of

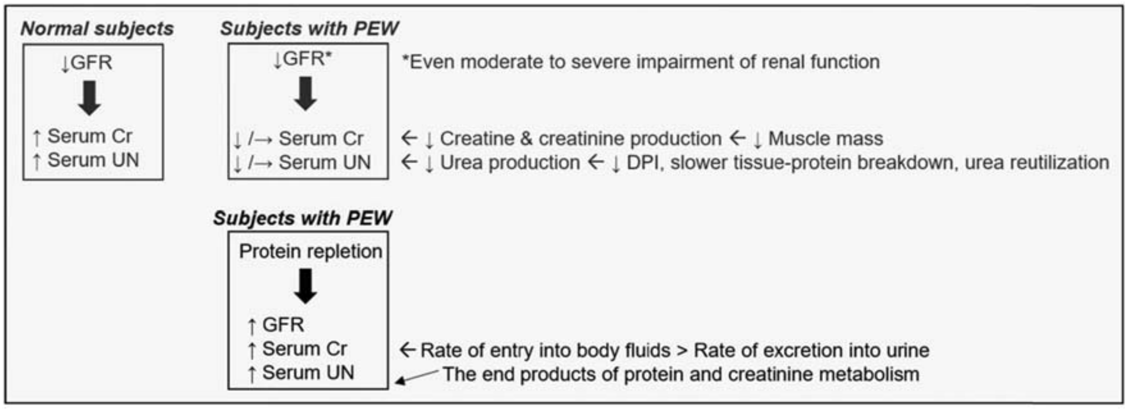
Normal subjects
↓GFR
↑ Serum Cr
↑ Serum UN
Subjects with PEW
↓GFR*
↓/→ Serum Cr
↓/→ Serum UN
*Even moderate to severe impairment of renal function
← ↓ Creatine & creatinine production ← ↓ Muscle mass
← ↓ Urea production ← ↓ DPI, slower tissue-protein breakdown, urea reutilization
Subjects with PEW
Protein repletion
↑ GFR
↑ Serum Cr
↑ Serum UN
← Rate of entry into body fluids > Rate of excretion into urine
The end products of protein and creatinine metabolism

FIGURE 15.3 Impact of PEW on serum creatinine and urea nitrogen levels. In patients without PEW, GFR impairment is manifested by higher levels of serum creatinine and BUN. However, in patients with PEW, serum creatinine and BUN levels have a tendency to be normal or low even in the context of moderately to severely impaired GFR due to (1) reductions in muscle mass and (2) decreased protein intake leading to reduced tissue−protein breakdown and urea reutilization. *BUN*, Blood urea nitrogen; *Cr*, creatinine; *DPI*, dietary protein intake; *GFR*, glomerular filtration rate; *PEW*, protein-energy wasting; *UN*, urea nitrogen.

reduced muscle mass and serum creatinine and urea production.

Protein-energy wasting and proteinuria

Several studies have examined the long-term impact of protein-energy wasting during the in utero period and in childhood upon risk of albuminuria, a marker of kidney damage and risk factor for GFR decline, cardiovascular disease, and death [197]. In a study of Dutch adults who had maternal exposure to famine at midgestation [198], there was a 3.2-fold higher risk of developing albuminuria compared to those without maternal exposure to famine, likely resulting from low birth weights and decreased nephron number. In another study of Brazilian children from the Centre for Nutritional Recovery and Education who were categorized as being well nourished, having stunted growth, being underweight, or having recovery from undernutrition, those in the stunted growth group had an 8.4-fold higher risk of developing albuminuria [199].

Protein-energy wasting and urinary concentration and dilution

Protein-energy wasting has also been associated with the development of polyuria and nocturia [200]; in this setting, increased urinary volumes have been observed in the context of impaired concentrating ability with preserved diluting capacity. In a study of adults with protein-energy wasting, the urinary concentrating and diluting capacities of which were examined before and after protein repletion [201], during the malnutrition phase, patients were found to have defects in urinary concentration, as shown by diminished maximal urine osmolality and solute-free water reabsorption. In contrast, urinary dilution was found to be preserved based on normal minimal urine osmolality and free-water clearance. Notably, patients' renal responses to the administration of exogenous antidiuretic hormone (ADH) were found to be adequate, and during protein repletion, there was an improvement in urinary concentration capacity (i.e., increased maximal urine osmolality and solute-free water reabsorption) in parallel with increases in urinary nitrogen excretion.

Impaired urinary concentration in patients with protein-energy wasting is likely a sequela of decreased renal medulla osmolality resulting from low concentrations of urea in the medulla [186]. With protein repletion the urinary concentrating defect slowly resolves, presumably due to a gradual positive nitrogen balance. However, urinary urea excretion may not rise for several weeks following an increase in dietary protein intake, suggesting that a rapid restoration in the renal medullary urea gradient and osmolality is not observed. In addition, replenishment of protein mass may lead to consumption of amino acids, leaving little for urea synthesis (i.e., anabolic effect) and a subsequent blunted increase in urea excretion. In contrast, oral intake of urea has been shown to lead to a rapid increase in the urinary concentration ability after 14 hours of fluid deprivation in malnourished subjects [186], suggesting the urinary concentrating impairments observed with protein-energy wasting are due to a functional defect as opposed to an anatomic abnormality.

Additional factors that have been implicated in the development of urinary concentration defects and polyuria in protein-energy wasting include (1) inhibition of ADH secretion by the posterior pituitary leading to decreased distal tubule reabsorption of water [200]; (2) decreased circulating amino acid levels (e.g., histidine, glutamate, and lysine) levels that enhance the hydroosmotic effect of ADH upon renal concentration capacity [202]; (3) enhanced α_2-adrenergic stimulation leading to impaired ADH-induced cAMP accumulation in cortical and medullary tubules and inability to excrete maximally concentrated urine in the hyperadrenergic state of protein-energy wasting [203,204]; and (4) decreased GFR, decreased medullary thick ascending limb sodium reabsorption due to increased prostaglandin synthesis, and increased papillary plasma flow [205].

Protein-energy wasting and acid–base disturbances

Protein-energy wasting has also been linked with acid–base disturbances. In healthy subjects, there is balanced acid production and excretion in steady state, and in the setting of an increased acid load/production from dietary intake (i.e., metabolism of dietary sulfo- and phosphor-proteins) and/or presence of organic acids, the kidney increases its excretion of acid to preserve acid–base balance. Among patients with protein-energy wasting, while normal blood pH and serum bicarbonate levels may be maintained during steady-state conditions, increased acid load/production may lead to greater severity of metabolic acidosis than observed in healthy subjects [206]. Adults [206] and children [207] with protein-energy wasting also have reduced acid excretion but typically maintain normal blood pH and serum bicarbonate levels due to decreased acid production. Indeed, the generation of hydrogen ions from metabolism, which is decreased in severe malnutrition, is typically related to protein degradation.

Research indicates that subjects with protein-energy wasting have an impaired response to acid loads [180,206]. For example, among patients with protein-energy wasting, administration of ammonium chloride (NH_4Cl) as an acid load resulted in a marked reduction in blood pH and plasma bicarbonate levels. The net acid excretion (NAE), defined as the sum of urinary ammonia plus titratable acid minus urine bicarbonate, was markedly decreased. Upon closer examination of NAE, although the basal production of urinary ammonia was low, the intrinsic capacity of the kidney to produce ammonia in response to an acid load was impaired. In contrast with ammonia, titratable acid did not appropriately rise with an acid load. This impaired response of titratable acid excretion following an acid load may have been due to deficiency in phosphorus, a buffer of titratable acid formation. Notably, when subjects with protein-energy wasting received a phosphorus infusion following administration of an acid load, an increase in titratable acid excretion was observed. These findings suggest that the impaired renal response to an acid load, or reduction in acid excretion, may be due to reductions in the urinary buffer, phosphorus, due to reduced dietary protein intake. Other factors contributing to impaired renal acid excretion in patients with protein-energy wasting include decreased ammoniagenesis [12], reduced gluconeogenesis [208,209], and altered transporter systems (i.e., lower proximal tubule Na^+/H^+ exchange [210], decreased distal proton secretion capacity [207,211]).

Protein-energy wasting and sodium retention

Protein-energy wasting is accompanied by impaired sodium excretion and sodium retention that may be improved with protein repletion [212]. This has been shown in a sodium-balance study of malnourished patients who were examined before and after protein repletion. While on a low-salt (10 mEq) diet, urinary sodium excretion was reduced to levels of ≤ 10 mEq/h. Upon consumption of a high-salt (170 mEq) diet, malnourished patients experienced a mean positive sodium balance of 400 mEq and weight gain of 2.8 kg after 5 days, whereas following protein repletion the same patients demonstrated a mean positive sodium balance of 150 mEq and weight gain of 1.2 kg on an identical diet [178].

Potential mechanisms contributing to impaired sodium excretion and sodium retention in protein-energy wasting include (1) hypoalbuminemia leading to decreased proximal sodium reabsorption due to reduced peritubular oncotic pressure; (2) impaired cardiac output leading to decreased peritubular hydrostatic pressure, decreased arterial blood pressure, and increased tubular reabsorption of salt and water; (3) decreased renal blood flow and GFR leading to reductions in the filtered load of salt and water; and (4) decreased renal blood flow and GFR leading to increased renin–angiotensin–aldosterone activity [213], thereby increasing the tubular reabsorption of salt and water [178,205].

Notably, in patients with severe protein-energy wasting who undergo dietary repletion, salt and water retention may also be observed with the development of refeeding syndrome. In this setting, insulin-mediated sodium reabsorption in the distal nephron may occur as a consequence of increased circulating insulin levels in the early phases of refeeding [214–216].

Effects of maternal nutrition on renal development

Maternal and paternal nutritional statuses have an important bearing on organ development and function, including that of the kidneys. Experimental animal models and epidemiologic data have shown that maternal malnutrition and/or low infant birth weights are linked with subsequent development of cardiovascular disease, hypertension, obesity, type 2 diabetes, the metabolic syndrome [217], as well as CKD and ESRD in later life [218].

Protein-energy wasting and renal development

Growing evidence has supported an association between exposure to maternal malnutrition and development of kidney disease. For example, findings from the Dutch Famine Study have shown that maternal exposure to extreme famine in midgestation is associated with increased risk of microalbuminuria in their adult offspring, presumably due to decreased formation of glomeruli [219]. In another natural experiment the impact of maternal exposure to the Chinese famine during gestation as well as in early postnatal life (i.e., first 2 years of life) was associated with higher risk of proteinuria in adulthood [220]. In contrast to the Dutch study that examined a previously well-nourished population upon whom famine was imposed, the Chinese study examined adults who had chronic malnutrition prior to famine exposure. However, the aforementioned studies should be interpreted with caution due to their methodologic limitations, including inadequate adjustment for key confounders (i.e., maternal health status, smoking status, weight) and unclear accuracy of reported maternal nutritional status [221].

Isocaloric protein restriction and renal development

Animal models of maternal isocaloric protein restriction (i.e., dietary protein intake accounting for 5%–12% of total energy intake) versus controls (i.e., dietary protein intake accounting for 18%–20% of total energy intake) during gestation have been consistently associated with lower birth weight, decreased nephron number, increased blood pressure, and kidney dysfunction in offspring [222–228]. To date, one human study has investigated the relationship between maternal protein intake and offspring kidney health [229]. In this study, higher maternal total and vegetable protein intake, but not maternal animal protein intake, during the first trimester of pregnancy were associated with higher eGFRs in childhood. However, first-trimester maternal protein intake was not significantly associated with childhood kidney volume, cystatin *C*–based eGFR, nor the risk of microalbuminuria. Protein restriction prior to conception [230] has also been shown to have long-term effects on kidney development. An experimental study of rats that underwent isocaloric protein restriction prior to conception followed by a control diet from onset of pregnancy demonstrated decreased kidney growth and lower relative kidney weights at 180 days [230]. In summary, early nutritional exposures in the pre- and peri-conception period and over the course of pregnancy have an important bearing on kidney growth and/or function in later life.

Conclusion

In summary, dietary macronutrients are key modulators of kidney health outcomes. While a large body of data demonstrate the major role of dietary protein intake on renal hemodynamics, kidney function, and renal morphology, further investigations are warranted to advance our understanding of the effects of other macronutrients (e.g., carbohydrate, fat) and dietary patterns upon kidney health and longevity. In addition, while a number of studies have shown the acute renal physiologic changes observed with protein-energy wasting, further research is needed to determine the long-term sequelae of sustained deprivation of macronutrients on renal outcomes.

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PART III

Nutrition and slowing of progressive chronic kidney disease

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CHAPTER

16

Dietary interventions to slow the progression of chronic kidney disease and improve metabolic control of uremia

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For many decades, it has been recommended that patients with kidney disease should modify their nutrient intakes. Depending on the disease, these advices are generally focused on salt, protein, potassium, calcium, phosphorus, alkaline derivatives, oxalates, citrates, products that engender uric acid, and obviously water or fluid intake. In this chapter, we will focus on the experimental and clinical effects of protein intake on kidney function in patients with a chronic reduction in glomerular filtration rate (GFR) who do not have end-stage kidney disease. We will address the potential benefits and risks of limiting the patient's protein intake to an optimal level, and how to monitor the actual intake of these diets. In addition, the clinical evidence that justifies such dietary interventions in patients with chronic kidney disease (CKD) will be discussed.

Assessing the progression of chronic kidney disease

One of the main questions that arise when investigators want to study nephroprotection is how the progression of kidney disease should be monitored. Experimental studies frequently present histological data such as glomerular sclerosis, tubular atrophy, and interstitial fibrosis in response to diet interventions. However, such data are not available in humans, since ethical reasons prevent the performance of serial kidney biopsies during dietary interventions. Since kidney failure is the ultimate consequence of progressive kidney disease, kidney function and its impairment is usually considered a key outcome measure in experimental as well as clinical trials. However, one of the main limitations of this approach is that renal function is directly affected by nutritional intake independently of injury to kidney tissue. Thus interpretation of traditional markers of renal function could be flawed by nutritional interventions. To illustrate this point, Levey et al. have summarized the renal function decrease during the Modification of Diet in Renal Disease (MDRD) study using different estimates of GFR, in both groups of usual and low-protein intake diets (Fig. 16.1). If we accept the 125I-iothalamate renal clearance as the gold standard for GFR measurement, it is easy to note that other traditional renal function markers are not as accurate measures of GFR and can lead to misinterpretation. Although it is not the aim of this chapter to present detailed information on how to monitor renal function in experimental and clinical studies, some brief comments related to nutritional influences may be warranted.

Serum creatinine has been extensively used to monitor renal function and to assess kidney disease in clinical trials [1]. It is now well established that serum creatinine or its derivatives are not accurate indicators of renal function [2]. Serum creatinine is produced by the muscle catabolism of creatine, 1.7% of the entire muscle creatine pool is converted to creatinine daily. This conversion rate does not appear to be extremely constant, since the daily variability in this conversion rate, in healthy volunteers, has been reported to range from 6% to 26% [3]. Serum creatinine is also affected by creatine and creatinine intake from cooked meat [4]. Indeed, those investigators reported that serum creatinine increased by as much as 50% from normal values within 2–4 hours after a meal containing 225 g of boiled beef [4]. The halftime to achieve

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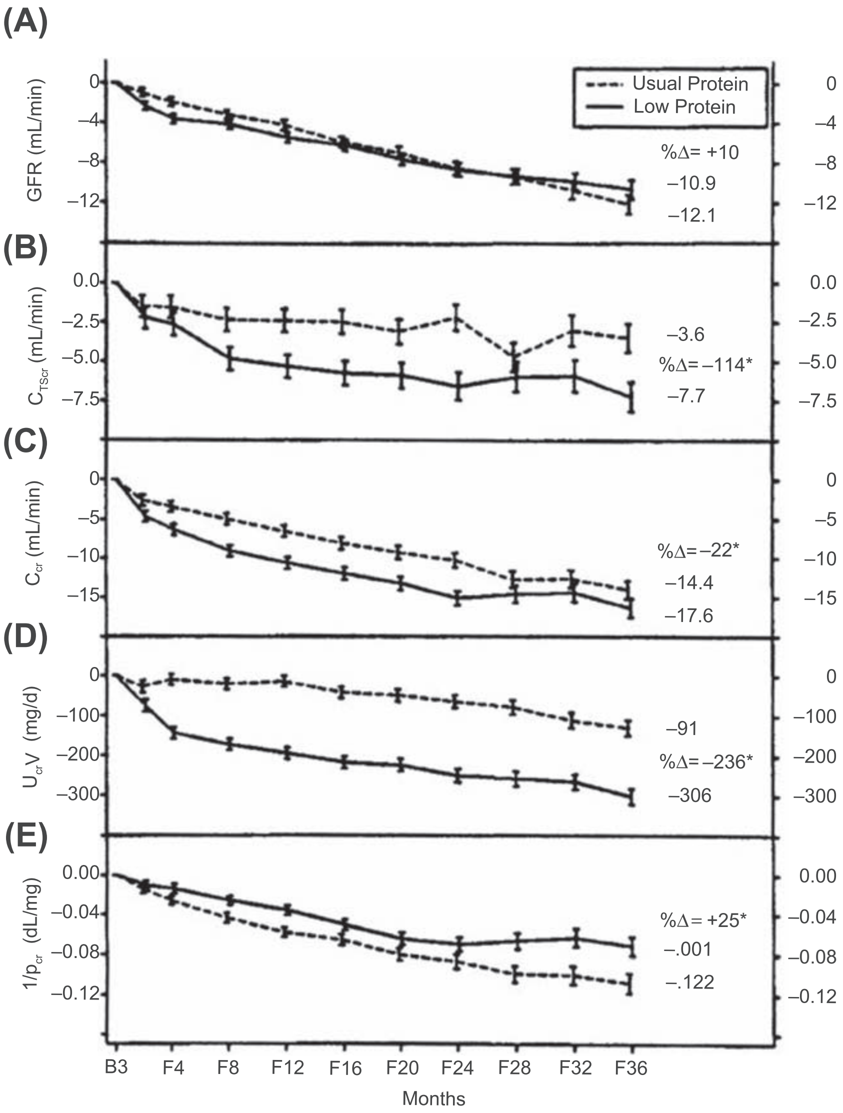


FIGURE 16.1 The rates of decline in renal function as measured by different techniques in Study A of the Modification of Diet in Renal Disease Study. Dashed lines: usual protein intake; solid lines: low protein diet. A: 125I-iothalamate plasma clearance; B: Tubular secretion of creatinine; C: Creatinine clearance; D: Creatinine excretion rate; E: Reciprocal serum creatinine. Source*: From Levey AS, Bosch JP, Coggins CH, et al. Effects of diet and antihypertensive therapy on creatinine clearance and serum creatinine concentration in the Modification of Diet in Renal Disease Study. J Am Soc Nephrol 1996;7(4):556-66.*

a new steady state in creatinine excretion following a change in creatine intake is 41 days [5]. Thus any change in creatine intake (e.g., in intake of animal skeletal muscle) will necessitate a minimum of three half-lives to reach a new plateau, for example, 4 months after the start of the new diet, and before any valid estimation of renal function from creatinine could be done. In addition, any change in the diet that leads to a variation of muscle mass will modify the creatine pool and creatinine production [6]. For instance, intensive physical exercise leading to hypertrophy of skeletal muscle will induce a rise in serum creatinine independent of renal function change.

Serum creatinine may also vary independently of renal function and food intake for additional reasons. First, there is intervariability between measurement techniques among different clinical laboratories that can exceed 30−40 μmol/L for the same sample. Second, the level of serum creatinine depends on the tubular secretion of creatinine, which has a great variability, particularly in the range of 40−80 mL/min of GFR [7]. In addition, the tubular secretion of creatinine is impaired by many medications such as trimethoprim, cimetidine, salicylate, or probenecid. These drugs will generally block the tubular secretion of creatinine, increasing serum creatinine without a change in GFR. Creatinine is also metabolized by extrarenal routes, mostly degraded by intestinal microorganisms, and this extrarenal clearance may vary as kidney disease progresses [8].

Since it has been showed that in most kidney diseases, there is a linear loss of renal function over time in more than 80% of patients, the inverse of serum creatinine (1/Secret), which also decreases linearly with time, has been used as a surrogate for estimating kidney function. Unfortunately, all of the limitations that exist using the serum creatinine as an indication of GFR also pertain to the reciprocal of the serum creatinine, thus rendering this marker unsuitable for assessing diet impact on renal function.

Creatinine clearance, serially measured, has been proposed as an indicator of kidney function loss. Creatinine clearance is not an ideal method for assessing glomerular filtration, since it exceeds the GFR by 10–15 mL/min (in healthy adults) due to active tubular secretion. As kidney function deteriorates further, the tubular secretion increases disproportionately and can overestimate kidney function by 80%–100% in cases of severe kidney insufficiency [7,9]. The correlation between the creatinine clearance and true GFR is weak and improves after administering cimetidine (800 or 1200 mg), which blocks the tubular part of creatinine clearance, 1–2 hours before commencing the urine collection [9–11]. In the pilot phase of the MDRD study, the mean correlation between the rate of change in creatinine clearance (24-hour urine collection) and GFR (125I-iothalamate clearance) was only 0.56 and 0.50 in Studies A and B, respectively [12]. Another important nonspecific cause of inaccurate estimation of kidney function by the creatinine clearance is an incomplete urine collection. This inaccuracy tends to improve when short-period repeated urine collections are done over a 3- to 4-hour period [10,13]. Thus to assess the effects of a given intervention on kidney function in a clinical trial, creatinine clearance can be used under the following conditions: the range of kidney function of patients should be wide, the treatment does not affect the tubular secretion of creatinine, and the clearance is measured during short periods [10,13]. Whether "cimetidine" creatinine clearance should be performed in diet intervention studies has not yet been validated but perhaps should be considered when true GFR measurements cannot be employed.

Recently, a number of formulas have been derived from creatinine and various parameters such as age, gender, and weight (Eq. 16.1) [14–16]. These formulas appear convenient to use, can be computed directly from simple software or pocket organizers, and have broad applicability for the general treatment of kidney disease. Levey and colleagues reanalyzed the data obtained through the MDRD study and proposed a formula based on serum creatinine, serum urea, serum albumin, age, gender, and ethnicity, which is more accurate than creatinine clearance or the Cockcroft–Gault equation (Eq. 16.2) [17].

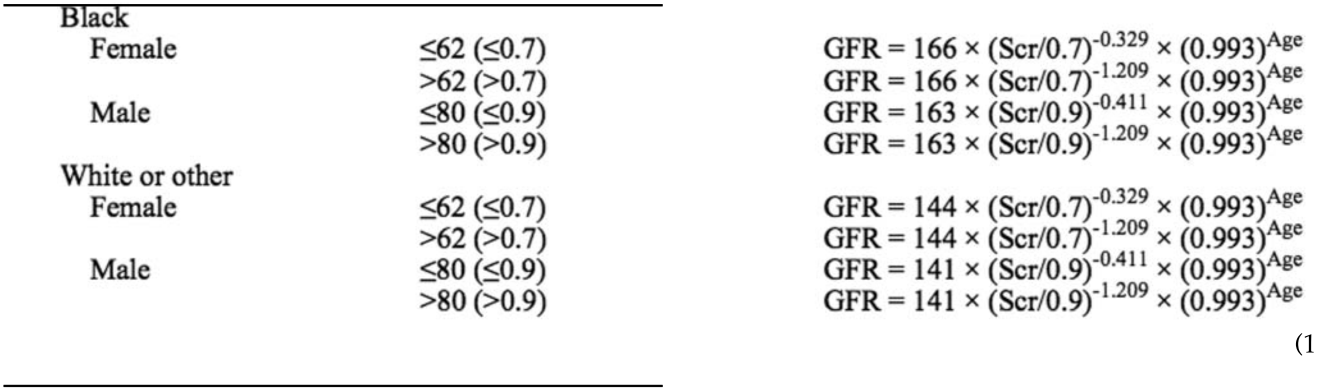
$$CCr = \left[(140 - age) \times Weight\right]/(Pcreat \times 72) \quad \text{for men} \tag{16.1}$$
$$CCr = \left[(140 - age) \times Weight\right]/(Pcreat \times 85) \quad \text{for women}$$

where CCr is creatinine clearance in mL/min, Pcreat is serum creatinine in mg/dL, age in years, and weight in kg (from Ref. [14]).

$$GFR = 170 \times [Pcreat] - 0.999 \times [Age] - 0.176 \times [0.762 \text{ if patient is female}] \times [1.180 \text{ if patient is black}] \times [SUN] - 0.170 \times [Alb] + 0.318 \tag{16.2}$$

where GFR is the GFR in mL/min/1.73 m^2, Pcreat is serum creatinine in mg/dL, Age in years, SUN is serum urea nitrogen in mg/dL, and Alb is serum albumin in g/dL (from Ref. [17]).

More recently, Levey et al. identified a new formula [18] called CKD-EPI (Chronic Kidney Disease - Epidemiology Collaboration), using different thresholds based on race, gender, and serum creatinine:



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	Female	≤62 (≤0.7)	GFR = 166 × (Scr/0.7)$^{-0.329}$ × (0.993)^{Age}
		>62 (>0.7)	GFR = 166 × (Scr/0.7)$^{-1.209}$ × (0.993)^{Age}
	Male	≤80 (≤0.9)	GFR = 163 × (Scr/0.9)$^{-0.411}$ × (0.993)^{Age}
		>80 (>0.9)	GFR = 163 × (Scr/0.9)$^{-1.209}$ × (0.993)^{Age}
White or other			
	Female	≤62 (≤0.7)	GFR = 144 × (Scr/0.7)$^{-0.329}$ × (0.993)^{Age}
		>62 (>0.7)	GFR = 144 × (Scr/0.7)$^{-1.209}$ × (0.993)^{Age}
	Male	≤80 (≤0.9)	GFR = 141 × (Scr/0.9)$^{-0.411}$ × (0.993)^{Age}
		>80 (>0.9)	GFR = 141 × (Scr/0.9)$^{-1.209}$ × (0.993)^{Age}

(16.3)

However, although simple formulas can predict GFR with acceptable precision for routine use (Cockcroft–Gault formula overestimates GFR by only 16%, e.g., 7 mL/min/1.73 m^2, [17]), for research purposes, more precise techniques should be used.

GFR is considered to be the gold standard for estimating renal function and for assessing the progression of kidney disease [2]. However, the GFR measurement is difficult to perform, expensive, and also presents some limitations. Traditional markers such as inulin have been challenged by radiotracers such as 125I-iothalamate, 99mTc-DTPA, or 51Cr-EDTA. Measurements can be done after a single injection, either subcutaneously or intravenously, and include plasma and/or urine samples over 3–4 hours. Usually, when urine samples are needed, bladder catheterization is not necessary but may be required in cases of bladder dysfunction such as in diabetes or neurological disease. To avoid prerenal azotemia, it is generally recommended to ensure a minimal urine output by ingesting a water load before the test. Anastasio and colleagues have challenged this fact while actually reporting a decrease in GFR after patients received a large oral water load (4 mL/kg body weight every 30 min) during a 3-hour GFR measurement [19].

Finally, another more pragmatic approach has been proposed recently to assess the efficacy of a treatment in kidney failure. The "renal death" was defined as the number of patients starting dialysis during a study [1]. Since it cannot formally be excluded that the death of a patient is not from kidney failure origin, we have included the number of death within the "renal death" definition, as well as the number of kidney transplantation before the start of dialysis if it happened during the study.

Protein intake and chronic kidney disease: Experimental data

There is ample evidence, dating from the 1920s, that elevated protein intake or amino acid infusion alters kidney hemodynamics and impairs renal function and tissue in normal animals or experimental kidney insufficiency [20–25] (for detailed reviews see [26–28]). In many of these experiments, it is somewhat difficult to clearly identify the specific role of protein per se, since sodium, energy, fluid, and phosphorus intakes obviously varied and were not always controlled. In addition, in the case of severe experimental nephropathy, high-protein intake may have elicited superimposed uremic toxicity and mortality not directly related to kidney function or kidney damage, thus adding confounding elements [21]. We will review here the experimental data on the renal effects of a reduced protein intake.

Effects on renal hemodynamics

The hemodynamic effects of dietary protein have been attributed to a number of mechanisms that eventually increase GFR, induce and/or increase proteinuria, and lead to glomerulosclerosis and kidney failure. Candidates for these mechanisms include hormones [glucagon, insulin, insulin-like growth factor-1 (IGF-1), and angiotensin II (AII)], cytokines (prostaglandins), and kinins [29–33]. Intrarenal regulation of sodium transport may also be involved through the proximal sodium/amino acid cotransporter; activity of this transporter is enhanced in response to an increased filtered amino acid load, thus stimulating the tubuloglomerular feedback and increasing the GFR [34]. Protein restriction ablates most of the hemodynamic changes observed after kidney ablation or 5/6 nephrectomy. Micropuncture studies provide direct evidence that the increase in single-nephron GFR after kidney mass reduction is responsible for the accelerated glomerular injury [35]. Reducing protein intake decreases GFR in normal animals and blunts the renal hemodynamic changes induced by extensive kidney ablation, that is, increased glomerular pressure and flow. Subsequent studies in rats with less severe kidney ablation showed that a low-protein intake also lowers hyperfiltration and retards the onset of proteinuria and glomerular fibrosis [23,36,37]. In addition to these experimental data, low-protein intakes also increased survival in these animals with reduced kidney function [21].

A reduced animal protein intake (usually a diet containing 6% protein) allows the control of glomerular hypertension by inducing afferent arteriolar vasoconstriction, which, in turn, decreases the glomerular plasma flow and reduces proteinuria [35]. Protein restriction decreases the percentage of glomerular sclerosis and proteinuria. Indeed, Hostetter and colleagues reported that at 4 and 8 months after the onset of kidney disease created by a 5/6 nephrectomy, glomerulosclerosis was attenuated by 50% in animals receiving a 6% protein diet and proteinuria was lowered to 25% of that in rats receiving a 40% protein diet [23]. Of importance, these benefits were observed at different levels of kidney disease (Fig. 16.2).

Micropuncture studies in 5/6 nephrectomized rats showed that a reduction in protein intake from 20% to

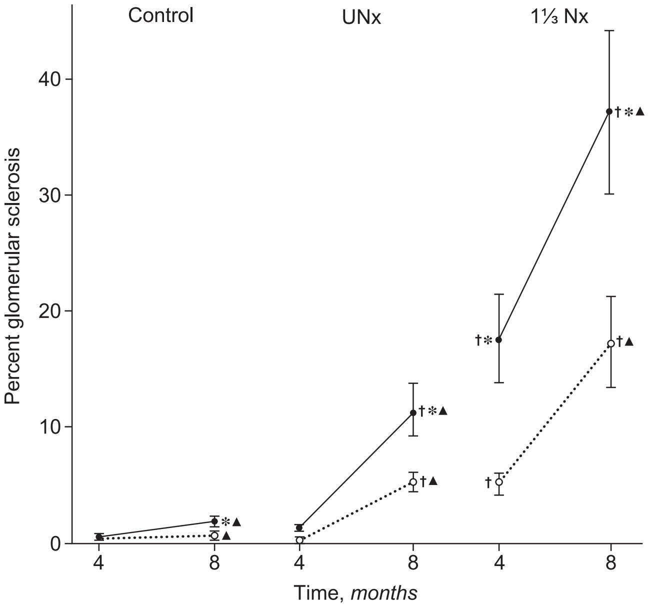


FIGURE 16.2 Percentage of sclerosed glomeruli in two different levels of experimental renal insufficiency as compared with a control group of rats. Open circles: low protein intake; close circles: high protein intake. Source*: From Hostetter TH, Meyer TW, Rennke HG, Brenner BM. Chronic effects of dietary protein in the rat with intact and reduced renal mass. Kidney Int 1986;30(4):509–517.*

6% led to a reduction in single-nephron GFR and intraglomerular capillary pressure to normal [25]. Of interest, proteinuria in the 6% protein diet group was reduced to one-fifth of proteinuria observed in the 20% protein diet group. Both groups of rats were hypertensive, and there was no discussion on what the effects of a low-protein diet would have been if the rats were normotensive [25]. Thus whereas a low-dietary protein intake shortly commenced after the onset of kidney ablation seems to mainly blunt the increase in glomerular capillary pressure, a delayed low-protein diet will reduce glomerular capillary pressure without lowering kidney hyperperfusion or hyperfiltration [25,38]. These data support the deleterious impact of glomerular hypertension, and the protective role of a low-protein intake on the remnant renal function in experimental kidney disease.

Effects on oxidant stress and inflammation

Protein intake and protein trafficking through the kidney are associated with hypermetabolism [39] and oxidant stress [40]. Oxygen consumption and ammonia production decreased by about 50% when rats were fed with a 12% instead of a 40% protein diet [40]. This fact is primarily explained by a decrease in net sodium reabsorption [41]. In another study, hypoxic injury of the thick ascending limb was mitigated by reducing the protein content of the diet [42]. Additional metabolic data obtained through 31P-NMR spectroscopy also show that protein restriction reduces intracellular inorganic phosphate and pH, consistent with a decrease in oxygen consumption [43]. This decrease in oxygen demand secondary to a reduction in protein diet from 30% to 6% may be responsible for reduced kidney production of glutathione and malondialdehyde [41,43].

Other studies have addressed the potential kidney antifibrotic effect of a low-protein diet. Nakayama and colleagues reported that in adriamycin-treated rats, expression of fibronectin and TGF-β in the kidney was dramatically reduced when animals received a 6% protein diet as compared with their littermates receiving a regular 20% protein diet [44]. In addition, these investigators showed a posttranscriptional reduction in fibronectin synthesis after short-term (2-week) treatment with a low-protein diet, whereas there was no difference in fibronectin gene expression. These interesting observations bear similarities to the effects of energy and protein intakes on the transcriptional and posttranscriptional regulation of IGF-1 synthesis in liver cells [45,46].

TGF-β, a potent profibrotic agent, is decreased by intervention with low-protein diets. Peters and colleagues documented two sets of findings in this regard: first, L-arginine supplement augmented the propensity of a low-protein diet (6%) to reduce the glomerular expression of TGF-β, fibronectin, and plasmin activator inhibitor 1 (PAI-1) in a model of immune glomerulonephritis [47], independent of nitric oxide metabolism. Second, whereas maximal AII blockade by very high doses of either ACEI (angiotensin converting enzyme inhibitor) or AII antagonists resulted in only a 45% decrease in TGF-β gene expression and protein production, the addition of a low-protein diet to other well-established nephroprotective treatments resulted in a further 20% reduction in TGF-β expression and production, and this was associated with a similar decrease in fibronectin and PAI-1 [48]. It should be emphasized that in both experiments the control of profibrotic mediators was associated with a concomitant decrease in proteinuria. These findings provide good evidence that a low-protein diet possesses its own therapeutic actions, independent from ACEI or AII antagonists on kidney scarring.

Tovar-Palacio and colleagues [49] studied the effects on kidney tissue of different amounts and nature of protein intake in obese Zucker rats. These animals that had normal renal function ingested either casein or soy protein, in an amount of 20%, 30%, or 45% of the food intake for 2 months. Urine excretion of hydrogen peroxide, a marker of oxidative stress, increased in a parallel manner to the protein intake, and for the same amount of protein in the diet, was consistently lower in the vegetal source of protein as compared with the animal one. Proteinuria followed the same trend and was lowest in the 20% soy protein diet [49]. Furthermore, kidney expression of genes involved in inflammation (IL-6 and TNF-α), lipid metabolism (SREBP-1 and FAS), matrix accumulation (type IV collagen), and fibrosis (TGF-β) was lowest in the 20% soy diet and highest in the 45% casein diet. Although these rats did not have kidney failure, these results strongly support a deleterious effect of high casein intake and a nephroprotective impact on low protein from vegetal source [49].

Studies have addressed the potential role of endothelin (ET) as a cause of puromycin-induced glomerulosclerosis. In addition, ET-1 gene expression has been reported to be elevated in other kidney mass reduction experiments. Nakamura et al. reported that a 6% protein diet was able to reverse proteinuria and increase ET receptor mRNA, ET-1 mRNA, and protein in puromycin-induced glomerulosclerosis as compared with rats receiving a 22% protein diet [50]. Whether this improvement occurs through a reduction in factors that stimulate ET release, for example, TGF-β and TNF-α, has not been directly proven in this experiment but represents a possibility [51].

Kruppel-like factor-15 (KLF-15) is a transcription factor that has been showed to reduce cardiac fibrosis. Gao et al. [52] studied KLF-15 in 5/6 nephrectomized rats receiving either a controlled (22%), or low-protein intakes (6% or 5% + 1% ketoacids) for 6 months. As expected, proteinuria, glomerular sclerosis, and tubular fibrosis were reduced in both LPD (low protein diet) and LPD + KA (ketoanalogues) groups, but to a greater extend in the LPD + KA rats [52]. Kidney expression of profibrotic factors (TGF-β, fibronectin, and type IV collagen) was dramatically reduced in both LPD groups, as were proinflammatory markers (TNF-α, MCP-1, and RANTES). As a consequence of increased TGF-β and TNF-α production in CKD rats receiving the control protein, KLF-15 expression was completely abolished, whereas LPD or LPD + KA almost restored KLF-15 expression to normal. For virtually all measurements, LPD + KA did improve KLF-15 better than LPD alone [52]. Thus there is an extensive data set to support the kidney antioxidant, antiinflammatory, and antifibrotic effect of a reduction in protein intake in experimental kidney disease.

Effects of the source of dietary proteins

As already shown earlier by Tovar-Palacio et al. [49], the effect of the type of protein deserves further comments. Based on the observation that vegetarians have lower GFR than omnivores [53,54], Williams et al. tested two different sources of protein derived from either animal or vegetable origin, casein, or soya, in stable CKD rats [55]. Both regular (24%) and moderately low (12%) protein intakes of each of those two protein sources were studied. After 3 months of dietary feeding, glomerulosclerosis and tubular dilation were found to be always greater in the casein- versus soya-fed groups. Proteinuria was greatest with the 24% [99 ± 34(sd) mg/day] and 12% (64 ± 18) casein diet, lower in the 24% soya group (30 ± 5), and lowest in the 12% (35 ± 7) soya groups. There was no difference in the severity of the proteinuria or histological lesions in the 24% versus the 12% soya groups [55]. Although these results are convincing, it should be noted that, due to the different digestibility of protein, it is possible that vegetable proteins were less absorbed than the animal proteins by about 10%, thus reducing the true protein load with the former diet. It is interesting to note that particular amino acids may elicit specific renal hemodynamic effects. A diet enriched with L-arginine, the precursor of nitric oxide (NO), has been shown to reduce glomerular hypertension and glomerulosclerosis in 5/6 nephrectomized rats [56]. Because NO is a potent vasodilation factor, locally enhanced NO production may be involved in these hemodynamic changes. L-Arginine also stimulates growth hormone secretion, which may also cause renal vasodilation through the release of IGF-1, and consequently, NO.

Protein and/or energy intake?

Venkatachalam and colleagues developed another interesting hypothesis. Since in most studies of protein reduction, it is the whole food intake that is reduced, these authors have studied the effects of energy restriction as compared with protein restriction [57]. Five groups of 5/6 nephrectomized rats were fed either a control diet, a 40% reduction in overall food, a 40% energy-reduced diet, a 40% protein-reduced diet, and a 40% salt-reduced diet. After 21 weeks of diet, histological findings clearly showed protected kidneys in the low energy alone group, which disclosed less glomerulosclerosis as well as less interstitial inflammation, as compared with all other groups. Of interest, proteinuria was lowest in this calorie-restricted group [57]. The discrepant finding of an absence of beneficial effects of the protein-reduced diet might be explained by a too modest reduction in protein intake as compared to the control diet. In a subsequent paper, these investigators reported that 2 weeks after 5/6 nephrectomy, the kidney IGF-1 content and the severity of inflammatory lesions were reduced with calorie restriction [58]. Altogether, these results suggest that IGF-1 expression could be involved in the tubulointerstitial inflammatory response and controlled by a low energy intake. Of interest is the fact that proteinuria was also reduced by the low-calorie diet [58].

In a strain of mice (kD/kD) developing an autoimmune interstitial nephritis, Fernandes et al. showed that a low-protein diet alone did not reduce mice mortality as compared with a combined protein and calorie restriction which induced the largest survival in animals [59]. However, the suppression of immune disease may be a more important cause of reduced mortality than any alteration in kidney metabolism or physiology in this experiment. Since in patients, reducing energy intake to a level that may induce malnutrition is not considered appropriate or justifiable, the relevance of these energy intake–reducing studies to clinical medical care may be quite limited.

It should be emphasized that the effects of a low-protein diet in reducing proteinuria may impact on tubular atrophy and apoptosis [60]. Indeed, there is a toxic role of serum albumin on tubular cells in culture [61,62]. Two sets of experiments have highlighted the role of protein delivery to the tubule in increasing interstitial fibrosis [63] and tubule cell apoptosis [64]. Indeed, the dramatic increase in proteinuria following intraperitoneal bovine serum albumin is associated with a profound tubular apoptotic reaction. Thus since most experiments have shown that reducing protein intake is associated with a reduction in proteinuria [65], it is possible but not proven that a low-protein intake also reduces kidney apoptosis.

In summary, there is a whole set of evidence from experimental research that high-protein loads are hazardous to the kidney, and that a large number of the physiopathological changes that occur secondary to reduced functioning kidney mass or kidney disease are corrected or, at most, improved by diets low in protein. However, these experiments use the extreme ends of dietary protein content, to identify these histological and hemodynamic changes. For example, Neugarten et al. reported that the kidney injury and proteinuria of puromycin-treated rats improved with a diet providing 4% protein, as compared with a group of rats receiving a 50% protein diet [66]. How do these extremely different protein diets compare with clinical studies? How would humans respond to low-protein diets? What is the evidence for the nutritional safety of low-protein diets? Could it be possible to adhere to such diets for long periods of time? How to monitor compliance? These questions will now be addressed.

Dietary protein intake: Clinical studies

Protein requirements in normal individuals

In the United States the daily average protein intake is about 90−110 g in adult men and 65−70 g in adult women, and 1.3 g/kg in most European countries. Protein intake tends to diminish by 15% by the age of 70 [67]. In women the mean protein intake is 30%−50% lower than in men for the same age [68] and is in accord with their 40% lower muscle mass as compared with men [69]. Thus based on the FAO recommendations, most adults in occidental countries have protein intakes far above the recommended allowance, which currently is 0.75 g/kg/day [70]. Furthermore, it should be emphasized that the 0.75 g/kg body weight value is defined as the safety level, including two standard deviations above the average requirement obtained through individual metabolic balances, thus guarantying that at least 97.5% of subjects will attain neutral or positive nitrogen balance [70]. Fortunately, due to the Gaussian distribution of protein requirements, many normal individuals will be in neutral protein balance with a lower level of protein intake. This fact may partly explain why in maintenance dialysis, patients, some individuals, present with nPNA (normalized protein nitrogen appearance) lower than recommended and show little or no signs of protein malnutrition.

In patients with CKD, from the perspective of the nutritional needs to maintain healthy body composition, there is no need to increase or decrease these recommended dietary protein levels. Indeed, in stable adult patients, most nitrogen balance and protein turnover studies have confirmed these data (see later). In addition, it should be noted that during the progression of kidney disease, spontaneous alterations in nutrient intake frequently occur, generally in the form of a reduction in both energy and protein intake [71−73]. Indeed, in an NHANES survey, it was reported that in patients with an estimated GFR between 30 and 60 mL/min, spontaneous energy and protein intakes were 23.3 ± 0.7 (sem) kcal/kg/day and 0.91 ± 0.03 g protein/kg/day, and in patients with a GFR less than 30 mL/min the values were 20.9 ± 1.0 kcal/kg/day and 0.86 ± 0.03 g protein/kg/day [74]. These findings are of particular clinical importance, because when there is a deficient energy intake, the body cannot adjust as readily to a reduction in protein intake. Thus in the absence of a dietary control and care plan, patients with CKD will nutritionally do worse than if they were enrolled in an optimal low protein and adequate energy intake diet [73,74].

In addition to this information, high-protein intakes have been shown to impair kidney function. Two large recent studies and one review have highlighted the deleterious effect of high-protein intakes on the progression of kidney damage [75−77]. Finally, the NephroTest study, another large-scale French prospective cohort of stage 3 CKD patients followed for up to 3 years, showed a linear positive association between protein intake (assessed independently by both urinary nitrogen output and dietary intake) and the need to start maintenance dialysis. Patients eating 1.2 g protein/kg/day had a 30% increase in dialysis need compared with patients with a protein intake of 0.6 g/day [78]. It should be noted that these patients were in a daily life cohort without any dietary advice or restriction.

Metabolic effects of low-protein diets in human

Metabolic adaptation to a reduction in protein intake

Fig. 16.3 shows the metabolic adaptation that occurs when an ad libitum protein diet (1.1 g/kg/day) is changed to a more limited protein intake (0.7 g/kg/day) in 12 patients with moderate CKD without the nephrotic syndrome [79]. Using a whole-body amino acid tracer (i.e., 13C-leucine), the investigators reported a net decrease in leucine oxidation, which is considered to reflect the excess amino acid catabolism; these findings suggest a normal adaptation in protein metabolism, similar to that reported in healthy volunteers [80]. There was no change in patients' body weight, serum albumin, or IGF-1 after the 3 months of this reduced protein intake, confirming the safety of this level of protein intake (0.7 g/kg/day) in CKD [79]. Other studies have reported similar findings in CKD patients undergoing different types of diet intervention but mostly with shorter studies. Goodship et al. studied six patients with moderate CKD during a short-term (1 week)

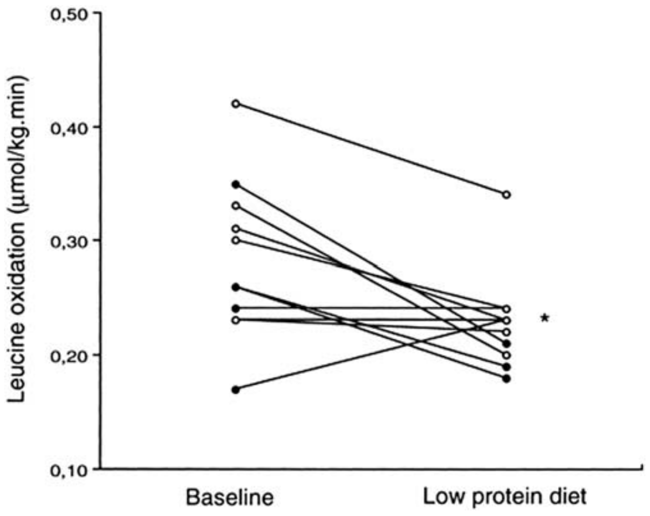


FIGURE 16.3 Total body leucine oxidation, a marker of protein metabolism, before and after ingestion of a low-protein diet for three months in 12 patients with moderate CKD (1.1g prot/kg/day in baseline vs 0.7 g/kg/day in LPD). The data demonstrate an adequate adaptation to a reduced protein intake (*p < 0.05 from baseline). Source: *From Bernhard J, Beaufrere B, Laville M, Fouque D. Adaptive response to a low-protein diet in predialysis chronic renal failure patients. J Am Soc Nephrol 2001;12(6):1249–1254.*

regular (1 g protein/kg/day) or reduced (0.6 g protein/kg/day) protein intake and with energy intakes of 32.5 kcal/kg/day [81]. Fasting leucine oxidation did not significantly change with the low-protein intake, whereas postprandial leucine oxidation decreased by about 25% ($P < .05$). As in nephrotic patients without chronic kidney failure [82], these data show that patients with mild kidney insufficiency can adapt their protein metabolism during acute or chronic reductions in protein intake by reducing amino acid oxidation during both the postprandial and the fasting state.

More restricted protein intakes have been shown to reduce amino acid oxidation by a greater magnitude. Masud et al. reported in six severe nondialysis CKD patients that a diet providing 0.35 g protein/kg/day supplemented with either ketoacids or essential amino acids for 25 days maintained neutral nitrogen balance and body composition [83]. These diets were associated with very low leucine oxidation rates that were not different whether patients were supplemented with ketoanalogs or essential amino acids [83]. In a long-term follow-up of these patients (16 months), the fasting leucine oxidation rate remained at the low level of 10.0 ± 2.2 µmol/kg/h [84]. In response to a lower protein intake, these values for amino acid oxidation appear to be more reduced than was observed in studies with less restricted protein intakes [79,81], suggesting a potential "functional reserve" for protein sparing in CKD patients.

Maroni and colleagues studied patients presenting with heavy proteinuria, for example, greater than 6 g/day, and moderate CKD (GFR, about 50 mL/min/1.73 m^2). Using leucine turnover and nitrogen balance techniques, they showed that a reduction from 1.85 to 1.00 g protein/kg/day in the patients induced adaptive protein conserving mechanisms that were similar to these of healthy volunteers and that the patients sustained positive nitrogen balance [85]. These results have been confirmed by Giordano et al. in seven patients with heavy proteinuria [82]; with a reduction in protein intake from 1.20 to 0.66 g/kg/day for 1 month, endogenous leucine flux decreased by 8% ($P < .05$), hepatic albumin synthesis decreased from 18.2 to 14.9 g/1.73 m^2 ($P < .03$) and serum albumin rose from 2.88 to 3.06 g/dL ($P < .03$).

In a more recent set of experiments, Garibotto and colleagues reassessed protein metabolism at the tissue level by forearm arteriovenous phenylalanine turnover in stage 3–4 CKD patients. In two different studies, they underwent 6-week diets in a crossover design with either a normal diet (1.1 g protein/kg/day) or two different low-protein diets (0.55 and 0.45 g protein/kg/day supplemented with ketoacids). Nitrogen balance was fully maintained during the study through an adaptive reduction in amino acid oxidation during the two low-protein diets [86].

Effects of low-protein diets on proteinuria

Since proteinuria has been clearly identified as an independent risk factor for the progression of kidney disease, it is relevant to examine the specific effects of low-protein diets on proteinuria. As discussed earlier, experimental studies almost unanimously report a reduction in proteinuria when animals are placed on a low-protein diet. In humans the acute 35% reduction in proteinuria observed by Rosenberg et al. [87] was confirmed during a longer duration of dietary therapy by Aparicio and coworkers [65]. These investigators reported a decrease in proteinuria from 3.2 ± 1.2 to 1.8 ± 1.1 g/day ($P < .01$) in 15 patients with advanced chronic kidney insufficiency after 6 months of a very low-protein intake (0.3 g/kg/day) supplemented with ketoacids, whereas serum albumin increased concomitantly from 36.5 ± 4.0 to 40.8 ± 3.2 ($P < .01$) (Fig. 16.4) [65].

In 12 proteinuric patients with CKD, Rosenberg and colleagues examined, in a random crossover design, the effects of a marked reduction in protein intake from 2 to 0.55 g protein/kg/day for 11 days [87]. There was a 35% decrease in proteinuria from 7.0 ± 3 to 4.7 ± 2 g/day, an improved glomerular permselectivity as determined by dextran clearances and from a disproportionate reduction in IgG as compared to albumin clearance, whereas there was no change in GFR and renal plasma flow [87], there was a net decrease in plasma renin activity and plasma

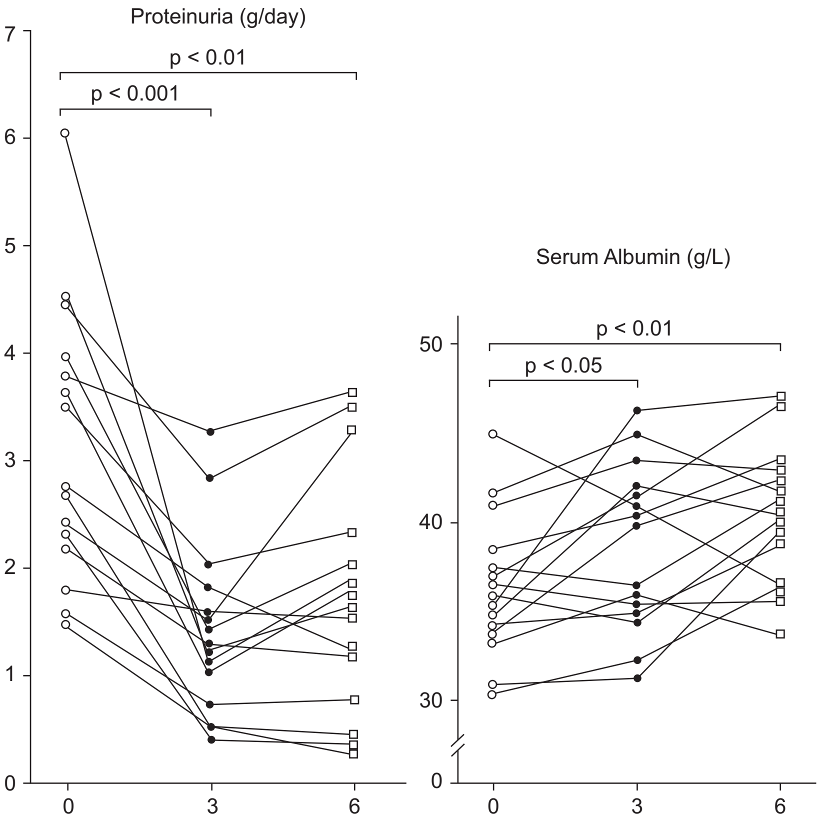


FIGURE 16.4 The decrease in proteinuria (left panel, g/day) and the increase in serum albumin (right panel, g/l) during three and six months treatment with a very low protein diet (0.3 g/kg/day) in 15 patients with advanced chronic kidney disease. Source: *From Aparicio M, Bouchet JL, Gin H, et al. Effect of a low-protein diet on urinary albumin excretion in uremic patients. Nephron 1988;50(4):288–291.*

aldosterone was also noted during the low-protein period, confirming experimental data.

When Giordano et al. [82] changed seven patients with the nephrotic syndrome from a 1.2 to a 0.66 g protein/kg/day protein diet, proteinuria decreased by 38%, and there was a linear relationship between the reduction in proteinuria and the achieved reduction in protein intake, as has been previously noted by Kaysen and colleagues [88]. It was proposed that a decrease in proteinuria is a stimulus for a reduction in albumin synthesis. Furthermore, fibrinogen synthesis rate also decreased by 30% with LPDs, from 4.6 to 3.0 g/1.73 m^2/day, $P < .03$; these synthesis rates, however, were still increased as compared with healthy volunteers (1.93 g/1.73 m^2/day) [82]. The similar reductions in albumin and fibrinogen syntheses may be triggered by a common mechanism, presently unknown, but which is advantageously modulated by a low-protein intake. Thus not only do patients with CKD generally adapt to low-protein diets but also there seem to be further benefits of such low-protein diets by reducing proteinuria and its consequent metabolic disturbances in nephrotic states. In another study, Bellizi et al. [89] reported in 110 CKD patients the effects during 6 months of three different protein intakes, 1.04, 0.78, and 0.54 g/kg BW/day, the last intake being supplemented with ketoanalogs. Proteinuria decreased significantly in the most restricted group, from 1.34 to 0.87 g/day, whereas it was not affected in the more important protein intake groups [89].

It is well established that ACE inhibitors and ARBs (angiotensin receptor blockers) markedly reduce the degree of proteinuria in most kidney diseases. Of interest is the additional antiproteinuric effect of a low-protein diet in combination with these nephroprotective medications. Ruilope et al. first described this observation in a short-term study involving 17 patients with mild CKD [90]. Enalapril, 20 mg/day, reduced proteinuria by about 20%; a 25% reduction in protein intake from 1 g/kg/day (estimated from urinary urea output) decreased proteinuria by 30%. However, the combination of both interventions induced a 55% decrease in proteinuria; this latter reduction in proteinuria was significantly greater than each separate intervention [90]. Gansevoort and colleagues [91] confirmed these findings by studying, in a crossover design, 14 patients with modest kidney impairment and nephrotic range proteinuria. Enalapril, 10 mg/day, induced a reduction of proteinuria by 35%, whereas a 50% reduction in protein intake decreased proteinuria by 20%. Again, there was an additional effect of both treatments, with a 55%–60% decrease in proteinuria by enalapril and low-protein intake. Furthermore, as shown in Fig. 16.5, there was a linear relation between the reduction in both protein intake and proteinuria [91]. A recent exhaustive

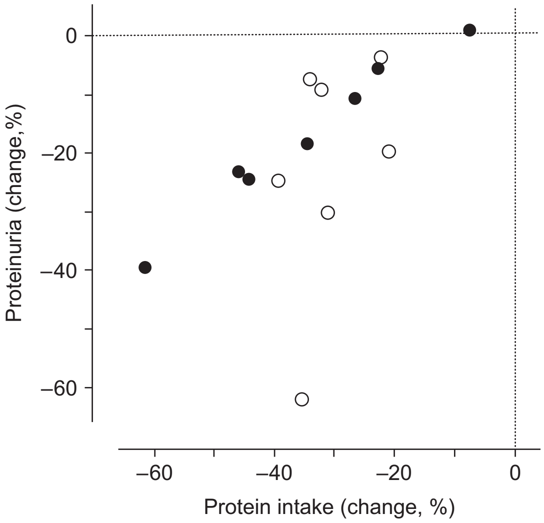


FIGURE 16.5 The linear relationship between the degree of reduction in dietary protein intake from baseline (1.0 to 1.5 g protein/kg/day) and the concomitant reduction in daily proteinuria in 14 nephrotic patients with normal to mild chronic kidney disease ($r = 0.58$, $p < 0.05$). Close circle: patients receiving a LPD only; open circle: patients receiving a LPD in addition to angiotensin converting enzyme inhibitors. Source: *Gansevoort RT, de Zeeuw D, de Jong PE. Additive antiproteinuric effect of ACE inhibition and a low-protein diet in human renal disease. Nephrol Dial Transpl 1995;10(4):497–504.*

review addressed the potential benefits of an LPD to those of ACEI/ARB-protective effects [92].

Effects of the nature of protein intake

As previously discussed in experimental studies, the nature of protein, for example, from animal or vegetal source, may impact on the kidney response to the diet [49]. In humans, Kontessis et al. examined the effects of protein of different sources on glomerular dynamics in 17 healthy volunteers. Although diets were not heavily restricted (intakes averaged about 1 g/kg BW/day), a decrease in GFR (−10%), in urinary albumin excretion (−50%), and IgG clearance (−35%) was observed after 3 weeks of ingesting a vegetable protein as compared to a regular animal protein diet [93,94]. In another study of similar design, these investigators measured GFR in nine diabetic patients without severe kidney involvement [93]. Again, there was a 15% and 40% decrease in GFR and in microalbuminuria, respectively, with the vegetable protein as compared with the animal protein diet. Interestingly, a marked decrease (−20%) in serum IGF-1, a strong GFR regulatory hormone, was also observed with the vegetarian protein diet, thus suggesting that protein intake might regulate renal hemodynamics, at least in part, through IGF-1 levels.

Another report from Brazil tested in 17 diabetic patients in a random crossover design, the effects of three different protein diets [95]. Patients had macro albuminuria and normal kidney function. One diet included beef protein, 1.33 g/kg/day, the second diet was composed of 1.22 g protein/kg/day from chicken meat, and the third was a low-protein diet of 0.8 g/kg/day from vegetable source. There was no change in GFR; macro albuminuria decreased from 313 μg/min (beef) to 269 (chicken) and 229 (vegetarian), $P < .05$. Lipid profile improved gradually as a consequence of a reduction in saturated fatty acid from red meat to low-protein diet. The authors attributed the reduction in macro albuminuria to the vascular protective effect of the polyunsaturated fatty acid enrichment mainly found in the low-protein vegetable source diet [95].

More recent data from the CRIC study addressed the metabolic effects of an increase in plant food in stage 3 CKD patients followed for 3 years. The lowest plant protein quintile group did show a higher urinary phosphate output compared with the highest plant protein intake quintile, suggesting a reduced phosphate absorption from vegetal source, whereas the total protein intake was similar between groups [96]. However, based on a large data set analysis, the recent AND/KDOQI guideline did not recommend to choose plant versus animal protein as a source of nutrients [97].

Effect of low-protein diets on insulin resistance

Abnormal insulin sensitivity and insulin resistance can be improved by a low-protein diet. Gin and colleagues tested the effects of a very low-protein intake (0.3 g/kg BW/day) in 10 patients with nondiabetic advanced CKD (creatinine clearance: 15 mL/min) supplemented by ketoacids on serum glucose and insulin after an oral glucose test. Both serum glucose and insulin peaks were significantly reduced after 4 months of diet (Fig. 16.6), suggesting an improvement in insulin resistance [98]. In a subsequent study, these authors investigated eight patients (GFR: 13.2 ± 2.8 mL/min/1.73 m^2) undergoing the same diet for 3 months [99]. Patients showed an improvement in fasting serum glucose from 5.0 ± 0.1 to 4.7 ± 0.1 mmol/L ($P < .05$), a decrease in fasting plasma insulin from 82.4 ± 20.7 to 48.8 ± 8.0 pmol/L ($P < .05$). More importantly, using the gold standard euglycemic insulin clamp, these workers showed a decrease in endogenous glucose production by 66% for comparable plasma insulin levels. These data clearly indicate an improved sensibility to insulin in nondiabetic CKD patients [99].

Effect of low-protein diets on dyslipidemia

As already mentioned, protein intake could be associated with different patterns of lipid intake. Mainly, meat intake brings saturated fatty acids (in pork, lamb, and beef), whereas white meat such as chicken or turkey bring less saturated fatty acids. Fish and vegetable proteins are mainly associated with

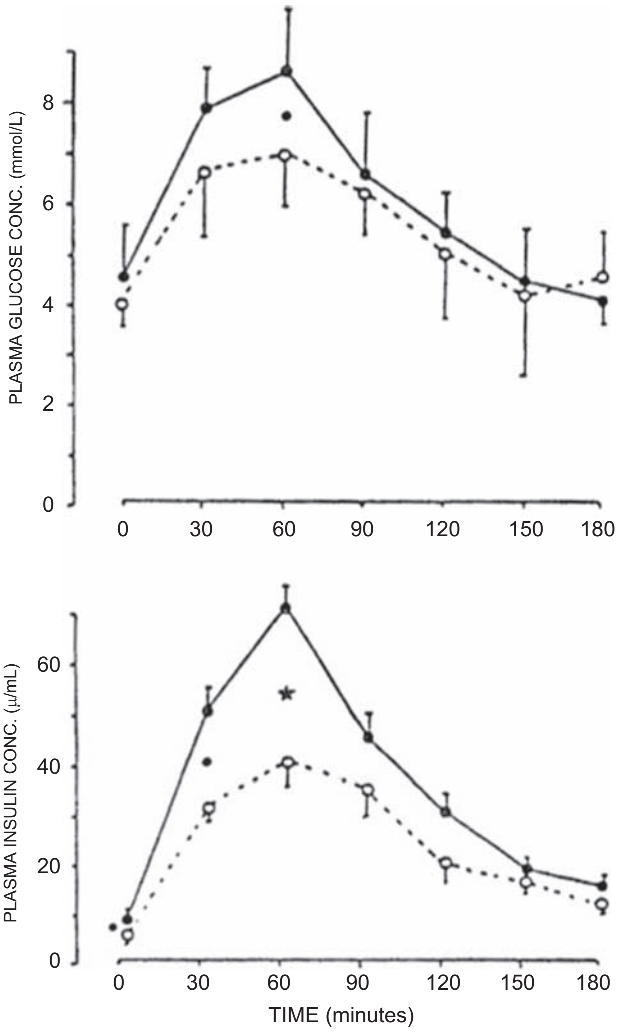


FIGURE 16.6 The effects of a reduction in protein intake during four months on plasma glucose and plasma insulin response (oral glucose test) in 10 non diabetic CKD patients. Protein intake was reduced from baseline (1.0 protein/kg/day) to 0.3 g protein/kg/day with ketoacids supplement. Baseline: close circle, low protein diet: open circle ($p < 0.05$). Source*: From Gin H, Aparicio M, Potaux L, de Precigout V, Bouchet JL, Aubertin J. Low protein and low phosphorus diet in patients with chronic renal failure: influence on glucose tolerance and tissue insulin sensitivity. Metabolism 1987;36(11):1080–1085.*

unsaturated cardiovascular protective fatty acids. In addition, cooking meat frequently bring extra lipid source and sodium chloride. As a consequence, most reports show that reducing protein intake from animal source improves lipid intake and patients lipid profile. For example, Bernard et al. reported an improvement in the ratio apoA1/apoB ($P < .03$) in 11 stage 3 CKD patients after they were switched from 1.1 to 0.7 g protein/kg/day during 3 months [100]. Bellizzi and coworkers reported a 24% and 18% decrease in serum total cholesterol and triglycerides respectively ($P < .001$), after 6 months of a very low-protein intake, which seems close to the effect of a statin treatment [89].

Effect of low-protein diets on phosphate, mineral, and bone disease

The mineral and bone disease field has emerged as one of the most important during CKD, not only because of progressive bone frailty but also because of a partial responsibility in increased vascular calcifications. Indeed, mortality from cardiovascular disease represents approximately 50% of the overall mortality at every stage of CKD, including the dialysis and transplant ones. Since hyperphosphatemia and hyperparathyroidism are frequently observed even at early stages of CKD, improving serum phosphate has long been the goal of a targeted dietary counseling before dialysis. Finally, the discovery of fibroblast-growth factor-(FGF)23, the key factor of phosphate metabolism, has reinforced the interest for research in this field.

Phosphate is strongly linked to protein since 1-g protein brings approximately 13-mg phosphate. Not all phosphate is absorbed by the gut, only 40%−80%, and this may be influenced by the fiber content of the diet, (i.e., phosphate from vegetarian source will be less absorbed than from animal source). By contrast, calcitriol will increase the fractional rate of gut phosphate absorption. Serum phosphate will also be influenced by kidney tubular excretion and bone metabolism. The different responses of phosphate metabolism during the progression of kidney disease have been highlighted in a recent work of Isakova and colleagues who notably showed that serum FGF-23 increases long before the rise in serum PTH (parathyroid hormone). Thus the primary response to the oral phosphate intake is an increase in serum FGF-23 to maintain a sufficient tubular phosphate excretion, for example, when GFR is about 80−60 mL/min. In addition, FGF-23 blunts the activity of the 1-α hydroxylase, blocking the synthesis of calcitriol in the proximal tubule and, therefore, reducing gut phosphate absorption. For yet unexplained reasons, during progressive CKD, FGF-23 fails to maintain normal serum phosphate and when GFR is about 50 mL/min, serum PTH starts to rise, which, in turn, compensates kidney phosphate excretion. Finally, when GFR drops below 35 mL/min, serum phosphate increases and there is no further efficient metabolic adaptation to this rise.

Why are these changes important to be highlighted in this section? First, in addition to the phosphocalcic abnormalities, it has been recently reported that elevated FGF-23 by itself may be independently linked to a reduced survival in healthy adults and CKD patients as well [101−103]. Second, the only way yet identified to improve serum FGF-23 is the reduction in phosphate intake, for example, protein intake. Indeed, in healthy adults, it has been reported that FGF-23 expression can be directly regulated by dietary phosphate. When adults received a daily oral load of 1-g phosphate for 5 days, serum FGF-23 increased by 30%, whereas serum PTH did not change. In response to the increased FGF-23, there was an increase in urinary phosphate excretion and a decrease in serum calcitriol, effectively counteracting the increase in dietary phosphate load [104]. Restricting dietary phosphate can also improve serum FGF-23: after 5 days of taking an oral phosphate binder, intestinal phosphate absorption decreased and urinary phosphorus excretion fell. Likewise, reducing the phosphate intake of 13 healthy men from 1500 to 625 mg/day induced a 30% decrease in serum FGF-23, suggesting that phosphate intake exerts a direct effect on FGF-23 expression [104].

Moe et al. studied in a random crossover design in nine stage 3 CKD patients the effects of two different diets with the same phosphate content, for example, 800 mg/day, one from animal source and the other from vegetarian source during 1 week [105]. They observed during the vegetarian diet phase the known reduction in urinary phosphate excretion and serum phosphate, in response to the reduced gut absorption of phosphate bound to vegetal fibers. More interestingly, they showed for the first time a significant 28% reduction in serum FGF-23 during the vegetarian cycle as compared with the animal protein phase during which FGF-23 increased by 40% ($P < .01$) [105].

These data emphasize why it is mandatory to monitor the dietary habits of CKD patients. Controlling serum phosphate below 1.4 mmol/L must include a phosphate-restricted diet. The daily amount of phosphate should be 800 mg, a level that allows enough dietary variety while protecting from excessive accumulation of phosphate. If dietary proteins are not controlled, even major increase in hormones controlling serum phosphate (PTH and FGF-23) will not be able to control the development of hyperphosphatemia.

Effect of low-protein diets on acidosis, anemia, and blood pressure

There are subsequent indirect beneficial effects of a reduction in protein intake during CKD on metabolic acidosis, hemoglobin status, and blood pressure control. Indeed, Chauveau et al. showed that there is an inverse relationship between protein intake and serum bicarbonate in a cross-sectional survey of more than 7000 hemodialysis patients [106]. In 10 stage 5 CKD patients receiving a supplemented very low-protein diet (VLPD) during 12 months, the same investigators showed an increase in serum bicarbonate from 24.2 to 26.5 mmol/L, $P < .05$ [107]. From the MDRD study, Mitch and Remuzzi also estimated that a reduction in 0.20 g protein/kg/day significantly increased serum bicarbonate ($P < .05$) [108]. These changes mainly pertain to the acidotic nature of animal protein, which was long identified by Claude Bernard in the late 1800s. Moving to vegetal protein will induce alkalotic urine, as observed in the majority of ruminant species. In light of recent De Brito's English trial, which convincingly demonstrated improvement in patients body composition and slowing of kidney disease progression after administering oral sodium bicarbonate [109], it may be also metabolically worth reducing animal proteins to increase serum bicarbonate.

Anemia control maybe improved while reducing protein intake. Indeed, Di Iorio et al. observed an improvement in hemoglobin levels in a random trial in 20 MHD patients receiving either a low-protein intake or a VLPD supplemented with ketoacids [110]. In the VLPD group, serum hemoglobin remained stable and erythropoietin dose could be decreased by approximately 35% during the 2-year duration of the trial. These investigators revealed a strong and inverse relationship between the change in patients' hemoglobin levels and serum parathormone, which is not unexpected since parathormone is responsible for a well-described resistance to the EPO (erythropoietin) effects on bone marrow. Improvement in parathormone was the consequence of the reduction of the dietary phosphate load and possibly to the calcium intake associated with the ketoacids. VLPDs should, therefore, be credited for these beneficial effects, although they could be considered as indirect.

Finally another dietary change that can be viewed positive is the fact that lowering animal protein will also reduce sodium intake, since most culinary habits do add salt while cooking meat. In the ERIKA study, a 6-month trial comparing three different levels of protein intake in [110] stage 4–5 CKD patients, Bellizzi et al. showed a positive relationship between 24-hour urinary sodium and urinary urea excretion, indicating that patients who ate less proteins had the most important reduction in sodium intake, and a better reduction in blood pressure [89]. As a consequence, patients will improve their blood pressure control and reduce their daily pill burden.

Nutritional safety of restricting protein intake

The question of whether LPDs are safe has been a subject of some controversy [111] and has been examined by estimating the nutritional status and survival of patients who received reduced protein intakes for years. Chauveau et al. [107] reported regional body composition measured by DEXA (dual x-ray absorptiometry) and nutritional status in 10 patients receiving a VLPD (0.3 g protein/kg/day supplemented with amino acids and ketoanalogs) for 1 year. There was no change in anthropometric measures and serum biochemistry during the 1-year follow-up [107]. DEXA analyses revealed a decrease in lean body mass during the first 3 months following the reduction in protein intake that was not fully corrected to baseline at 1 year (baseline: 46.2 kg; 1 year: 45.1 kg). Body fat mass increased slightly at 3 months and 1 year (baseline: 20.1 kg; 1 year: 21.4 kg, $P < .01$). Interestingly, there seemed to be a redistribution of lean body mass in favor of an increase in lean truncal mass, which was sustained during the 1 year of follow-up [107]. It should be mentioned that during this trial, energy intake was 27.8 ± 7.6 at baseline, 31.0 ± 8.1 at 3 months, and 29.8 ± 8.8 kcal/kg/day at 1 year. Thus the alterations observed after 3 months of a very low-protein intake spontaneously improved over time, became of no clinical importance after 1 year of follow-up, and occurred in association with the benefits observed with regard to insulin resistance, bone metabolism, and reduction in uremic symptoms [107]. Long-term low-protein interventions have also been reported to be safe by other investigators [112–116]. In the MDRD study, body weight and composition were assessed every 3 months during the 2.2-year mean follow-up period [116]. The actual reductions in protein intake were less than expected (actual vs prescribed: 0.71 vs 0.58 and 1.11 vs 1.3 g/kg BW/day, respectively, in Study A; 0.48 vs 0.28 and 0.72 vs 0.58 g/kg BW/day, respectively, in Study B). Furthermore, energy intake was low despite intensive counseling (range: 22.5–26.7 kcal/kg/day among different subgroups). Despite these values, overall clinical and biological surveys, as well as end point recording did not show evidence for nutritional impairment during a follow-up period of 2–3 years [116]. Fig. 16.7 shows that serum albumin levels increased slightly in all groups from baseline, but this increase was greater in the low-protein diet group as compared with the control group in Study A (Fig. 16.7, top, *solid line*). The decrease in serum transferrin during the study is somewhat difficult to interpret, because iron stores and the presence of inflammation were not monitored. Finally, although statistically significant, these changes in body composition may not be of clinical importance (−2 to 0 kg for body weight and −0.5 to +0.5% for body fat mass over 3 years). They underscore the importance for the physician to ensure that there is adequate nutritional monitoring and, where indicated, nutritional intervention in these patients (Table 16.1). Importantly, no patient had to withdraw from the MDRD study because of impaired nutritional status.

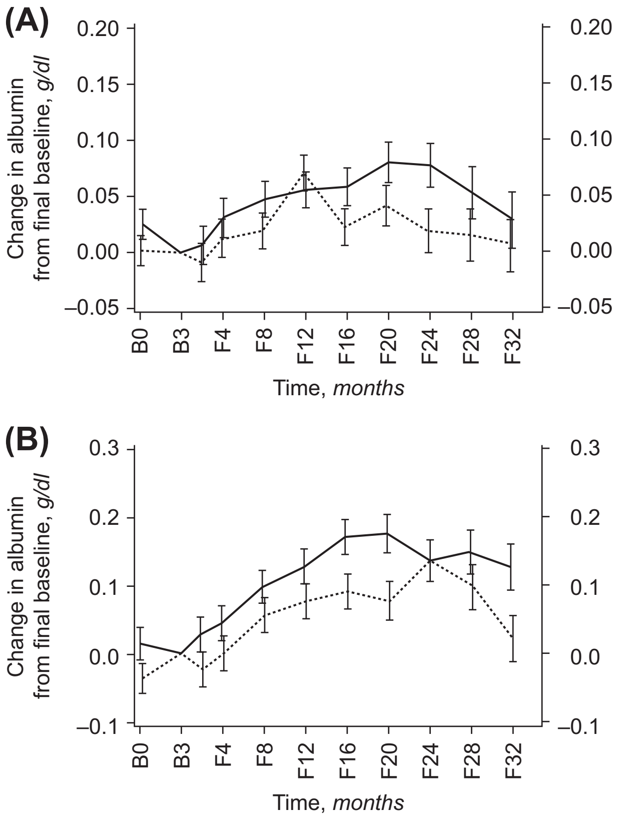


FIGURE 16.7 Mean changes in serum albumin from the end of Baseline in Study A (top) and Study B (bottom) patients during the course of the Modification of Diet in Renal Disease Study. From Kopple et al. (116) with permission. Source*: From Kopple JD, Levey AS, Greene T, et al. Effect of dietary protein restriction on nutritional status in the Modification of Diet in Renal Disease Study. Kidney Int 1997;52 (3):778–791.*

TABLE 16.1 Estimation of dietary protein intake (DPI) in a stable noncatabolic 70 kg adult patient undertaking a 0.6 g protein/kg/day diet, based on a daily urinary nitrogen appearance.

UNA = 4.8 g/day

DPI = 7.25 UNA + 10.9 = 45.7 g/day

DPI/kg = 45.7/70 = 0.65 g/kg

Compliance to the diet, for example, an upper actual protein intake no greater than 20% above prescribed intake, is considered acceptable if this patient presents a UNA no greater than 5.5 g/day.
From Kopple J.D., Gao Z.L., Quing .D.P., Kidney Int 1997;52:486–94.

The recent AND-KDOQI guideline assessed the nutritional safety of low-protein diets and concluded that neither low-protein diets nor supplemented VLPDs have been associated with impairment in nutritional status assessed by anthropometry, subjective global assessment, or serum albumin [97]. There was only 1 study among 26 randomized controlled trials that reported a significant loss in body weight (lean and fat mass) [112]. Nutritional status was also assessed by Hahn et al. in a recent Cochrane systematic review (see later) in which weights were available in more than 500 patients, and it was concluded that no significant change in body weight occurred during a follow-up of 12–50 months [1].

What is the long-term consequence of low-protein diets on survival after dialysis therapy is started?

Walser et al. demonstrated that patients ingesting a VLPD who were carefully followed before they commenced dialysis treatments could postpone dialysis for many months, even with very low GFRs, before clinical symptoms occurred [117,118]. Aparicio and colleagues reported encouraging outcomes in 165 maintenance dialysis patients who were treated with VLPDs before they developed end-stage kidney disease [115]. Chauveau et al. more recently reevaluated 203 patients long-term survival after they started maintenance dialysis or received a kidney transplant [119,120]. Analyzing these patients with an unbroken follow-up during 10 years after the start of replacement therapy, these authors clearly showed that patients who received an SVLPD (supplemented very low protein diet) before ESRD (end stage renal disease) had a survival as good as patients without specific diet as reported in the French Dialysis registry, for example, 79% at 5 years and 63% at 10 years [120]. Their results stand in contrast with those of Menon et al. who reanalyzed the late patients' survival of the supplemented VLPD subgroup of the MDRD study [121]. Although patients who received the SVLPD had a poor survival 7 years after the termination of the MDRD study, there was no clinical or biological information on patients to document survival during those 7 years and it is difficult to incriminate 30 months of well-followed dietary intervention versus 80 months of virtually unknown follow-up [119].

Clinical evidence of the effects of low-protein diets

For many years, it has been proposed that patients with advanced kidney disease should reduce their protein intake to decrease uremic symptoms. In the mid-1970s, since a number of experimental studies reported beneficial effects of low-protein intakes on kidney function, it was proposed to test this hypothesis in humans. Before analyzing in detail these studies, some general remarks should be made. First, as discussed earlier, most animal research studies were performed using extremely high or low levels of dietary protein (e.g., unphysiological or very large differences in dietary protein content between groups), to identify mechanisms and explain therapeutic effects. Second, in many experiments, substantial numbers of animals died without analysis of the potential role of the diet in these deaths. Only data from the survivors were analyzed, a fact that would not apply to human research. Third, most laboratory research is short-term, in animals that do not have other chronic diseases, by contrast with many patients presenting with CKD. Thus the issue of low-protein diets in CKD patients may differ from experimental studies. Indeed, as compared with experimental research, there are specific caveats to clinical research, such as the variability of outcome, the issue of treatment compliance and medication effects, and, eventually, the phenotype of the population studied. These factors are among reasons why such large numbers of patients are required to test a single hypothesis in a clinical trial.

Clinical trials and cohorts

A recent prospective observational study in France followed more than 1400 CKD stage 3–4 patients over 3 years [78]. No specific dietary counseling or nutritional target was provided. The number of patients starting maintenance dialysis was inversely related to the daily protein intake which was reliably assessed by both dietary reports and urinary nitrogen output. Patients with an average protein intake of 0.6 g/kg/d had a 25% lower dialysis need compared with those ingesting 1.2 g/kg/day [78] (Fig. 16.8).

More than 55 prospective clinical trials have assessed the effects of low-protein diets in humans with kidney disease. These studies have been analyzed in a recently updated review [1]. However, in many of these trials, the methodological quality was judged to be poor, based on uncontrolled design, nonrandom

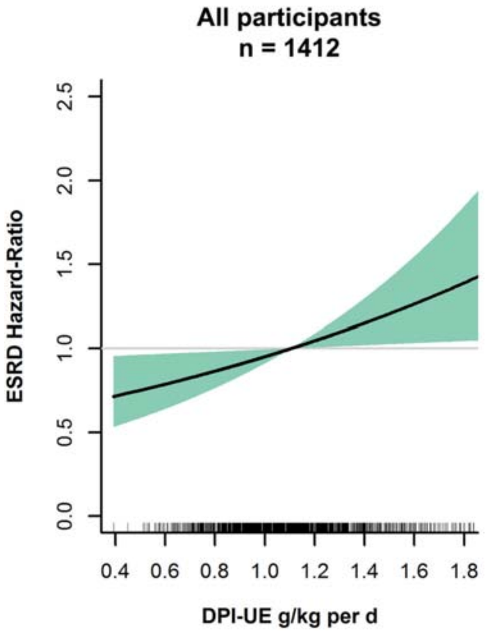


FIGURE 16.8 The inverse relationship between daily protein intake estimated by urinary nitrogen output and the hazard ratio for starting maintenance dialysis in the NephroTest prospective cohort. Source: *From Metzger M, Yuan WL, Haymann JP, et al. Association of a low-protein diet with slower progression of CKD. Kidney Int Rep 2018;3 (1):105–14.*

allocation of diets, or the use of retrospective analyses. Furthermore, many of these reports, undertaken in the early 1970s, did not use an adequate marker of renal function to assess the effect of the diet intervention, particularly since the serum creatinine or its derivatives (creatinine clearance, 1/serum creatinine) are strongly influenced by the primary intervention, for example, reducing protein intake (see earlier). Since contradictory results were often reported, we only reviewed the largest trials of high methodological quality, that is, those large prospective, controlled trials with a random allocation of diet intervention.

The Northern Italian Cooperative Study Group, in 1991, reported the results of a large randomized controlled study in 456 patients with a GFR lower than 60 mL/min, who were followed for 2 years [122]. Patients either received a control protein intake of 1 g/kg/day or a low-protein intake providing 0.6 g/kg/day, both diets provided an energy intake of at least 30 kcal/kg/day. The main outcome criterion was the renal survival defined as the start of dialysis therapy or the doubling of serum creatinine during the trial. Dietary protein intake was serially monitored by urinary urea output in a random sample of patients. Actual protein intakes were, however, poorly different since the control group did eat 0.90 g protein/kg/day and the low-protein group 0.78 g/kg/day, and there was a large overlap between individuals from both groups (underlining the necessity for intensive dietary counseling and monitoring). There was only a borderline significant difference between control and restricted protein groups with slightly less patients in the latter group reaching a renal end point ($P = .059$).

The MDRD study was the largest clinical study yet performed to test the effects of low-protein intake and strict blood pressure control on the progression of kidney disease in more than 800 patients [71,123–130]. Two groups of patients were studied, one with moderate kidney dysfunction (Study A, GFR: 25–55 mL/min/1.73 m^2) and the second with a more advanced kidney dysfunction (Study B, GFR: 13–24 mL/min/1.73 m^2). The patients were randomized to receive 1 g protein/kg/day or more versus 0.6 g/kg/day and to reach a mean blood pressure of 105 or 92 mmHg in group A, and 0.6 g protein/kg/day versus 0.3 g/kg/day plus a ketoacid supplement and comparable blood pressure goals in group B. The primary objective was the effect of both interventions, in a Latin square design and intention-to-treat analysis, on the progression of kidney disease. This was estimated by the changes in 125I-iothalamate clearance measured every 4 months over more than 2 years. The mean patient follow-up was 2.2 years [126]. Actual protein intakes were 1.11 ± 0.19 versus 0.73 ± 0.15 g protein/kg/day in group A ($n = 585$), and 0.69 ± 0.12 versus 0.46 ± 0.15 g protein/kg/day in group B ($n = 255$). The overall results appeared at first glance somewhat disappointing. There was no difference between the groups with regard to the decline in GFR in Study A. In Study B, there was a borderline significantly greater rate of decline in GFR in the group prescribed the 0.6 g protein/kg/day diet versus the ketoacid supplemented diet ($P = .07$).

These raw results require several comments. First, as shown in Fig. 16.9, during the first 4 months of diet intervention in Study A, there was a sharp initial decrease in GFR in the group with the more restricted protein intake (mean DPI, 0.73 g/kg/day). This was followed by a slower linear decrease than occurred with the larger protein intake (mean DPI, 1.11 g/kg/day). This initial 4-month decrease in GFR with the lower DPI is now considered to be the consequence of the reduction in glomerular hemodynamics that

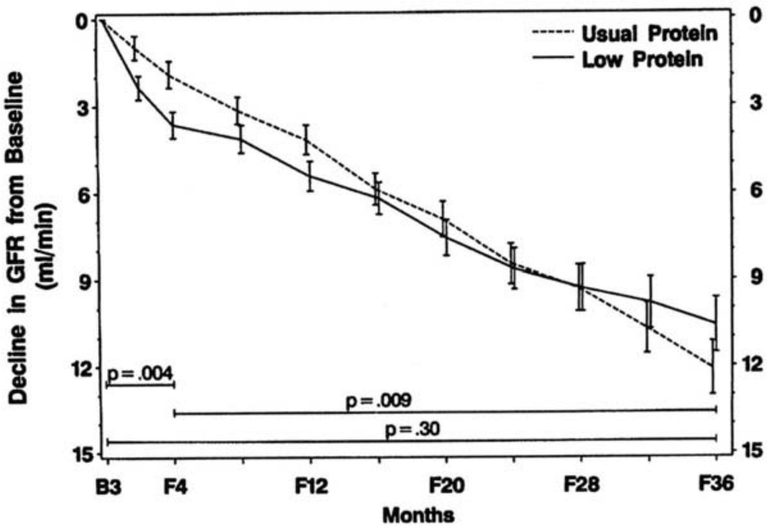


FIGURE 16.9 The GFR decline during the course of the Modification of Diet in Renal Disease Study (Study A) with separate analyses including or not the first 4-month adaptation period. *GFR*, Glomerular filtration rate. Source: *From Levey AS, Greene T, Beck GJ, et al. Dietary protein restriction and the progression of chronic renal disease: what have all of the results of the MDRD study shown? Modification of Diet in Renal Disease Study group. J Am Soc Nephrol 1999;10(11):2426–39 with permission.*

follows protein restriction [28]. Arguably, in retrospect, there should have been a run-in period that included the first several weeks of dietary protein treatment before the key GFR outcome data began to be collected. If this had been done, the follow-up period of the study, for example, from 4 months after the start until 3 years, the slope of GFR decrease, which was significantly lower in the more restricted protein group (Fig. 16.9, $P = .009$) [130], would have indicated a beneficial effect of dietary protein restriction in reducing the rate of decrease in GFR. Second, unexpectedly, the actual rate of progression of kidney failure was lower than expected when the study was designed (i.e., in Study A, the reduction in GFR was 3.8 vs 6 mL/min/year) [124]. This had a major negative impact on the ability of this study to demonstrate statistical differences. An additional 3-month period of follow-up would have been necessary to correct for this reduction in GFR decline. Thus it is tempting to classify this large clinical trial as inconclusive rather than negative. In addition, when patients were followed in an open fashion after the end of the study and up to 44 months of diet, the difference in cumulative incidence of ESRD or death reached borderline significance in the patients who were assigned to the lower protein diet ($P = .056$, Fig. 16.10). It should be remembered that in the large diabetes DCCT trial for strict blood glucose control and its effects of kidney impairment, no effect was detected at 2 years, and the suppressive effect of strict glucose control on the development of microalbuminuria or proteinuria was only observed after 4 years of treatment [131].

Although not definitive, correlational analyses may give further insights into the efficacy of dietary intervention, particularly when a flawed design, such as an observation period of inadequate duration, hampers the interpretation of the main outcome measure. First, when patients were analyzed with regard to their actual protein intake, as estimated through either diet interviews and diaries or urea nitrogen appearance, and independently of the group to which they were randomized, a strong relation was found between the magnitude of protein intake and the GFR slope ($P = .011$) or renal death (e.g., risk of death or ESRD) ($P = .001$) [130]. Indeed, for Study B, a regression model estimated that for every reduction in 0.2 g protein/kg/day, there was a 1.15 mL/min/year reduction in GFR decline and a 49% reduction in the incidence of renal death [130]. There was no additional effect of ketoanalog supplements on retardation of progression of renal failure. This finding contradicts a previous observation made in the MDRD Feasibility Study in which a trend for a protective effect ($P = .06$) of ketoacids was observed [129]. These latter authors suggested that the different ketoanalog composition used in the MDRD Study B, and particularly the greater tryptophan content, may account for the lack of effectiveness of the ketoacids in the MDRD study [129,132].

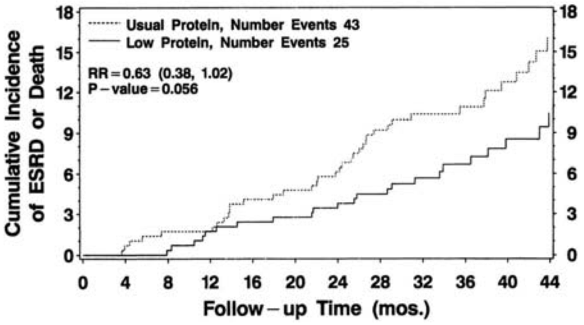


FIGURE 16.10 Occurrence of renal failure or death in Study A of the Modification of Diet in Renal Disease Study, including a 10-month additional follow-up after completion of the study ($P = .056$ between the two levels of protein intake). Source: *From Levey AS, Greene T, Beck GJ, et al. Dietary protein restriction and the progression of chronic renal disease: what have all of the results of the MDRD study shown? Modification of Diet in Renal Disease Study group. J Am Soc Nephrol 1999;10(11):2426–39 with permission.*

A comparable analysis in Study A showed a more moderate impact of protein restriction with a 0.32 mL/min/year slower GFR decline per each 0.2 g protein/kg/day reduction ($P = .075$). Thus these secondary analyses of the MDRD study tend to support a moderate beneficial effect of reduced protein intakes in patients with CKD; these effects were related, in a gradient fashion, to a reduction in the protein intake rather than to a well-identified degree of protein restriction that was necessary to slow progression. There was no apparent effect of either protein intake or blood pressure control in patients with polycystic kidney disease. Since these individuals constituted 25% of the total patients in the MDRD study, this fact also contributed to the ambiguous results of the MDRD study [133].

More recently, Garneata et al. [134] reported an elegant randomized controlled trial in 207 stage 4 CKD patients, with a GFR of 18 ± 3 mL/min, treated during 15 months. There was a two-steps selection of patients, one to identify those patients who would be able to comply with a protein restriction (782 among 1413 patients), and then a 3-month run-in period with a vegetarian diet test. After this test diet, only 207 patients qualified to enter the study and were randomized to receive a diet of 0.6 g protein/kg/day (control arm) or a 0.3 g protein/kg/day supplemented with a mixture of amino acids and ketoacids (0.125 g/kg/day) (intervention group). Energy intake was reported to be 30 kcal/kg/day during the entire study in both arms. It is important to note that after randomization, there was a 3-month initial adaptation period after which all measures started to be recorded for a further 12-month assessment time. This point is of major importance to allow the body to adapt to the hemodynamic and nutritional changes that occur after changing the protein intake. This aspect was not considered during the MDRD study (Fig. 16.9) and was primarily responsible for the 128 negative results published in the initial MDRD study report [126].

The study showed a beneficial effect of a very low vegetarian supplemented protein intake (VLPD) with 13% of patients reaching the end point (dialysis initiation or a >50% reduction in GFR) versus 42% in the LPD group ($P < .001$). Dialysis initiation alone was reported in 11% (VLPD) versus 30% (LPD), ($P < .01$). The prescription of nephroprotective medications (ACEI and ARB) was similar (approximately 70%) in both groups during the entire study. A detailed nutritional assessment did not report any difference in subjective global assessment, body mass index, anthropometry measures, serum albumin, and potassium. Acid–base metabolism was improved since serum bicarbonate rose from 16.7 to 22.9 mmol/L ($P < .01$) and bicarbonate supplements were noticeably reduced ($P < .01$) in the VLPD group as compared with the LPD group. Serum calcium and phosphate were also better maintained in the VLPD group during the entire study. Only 3% of patients left the study in equilibrium between groups.

Metaanalyses

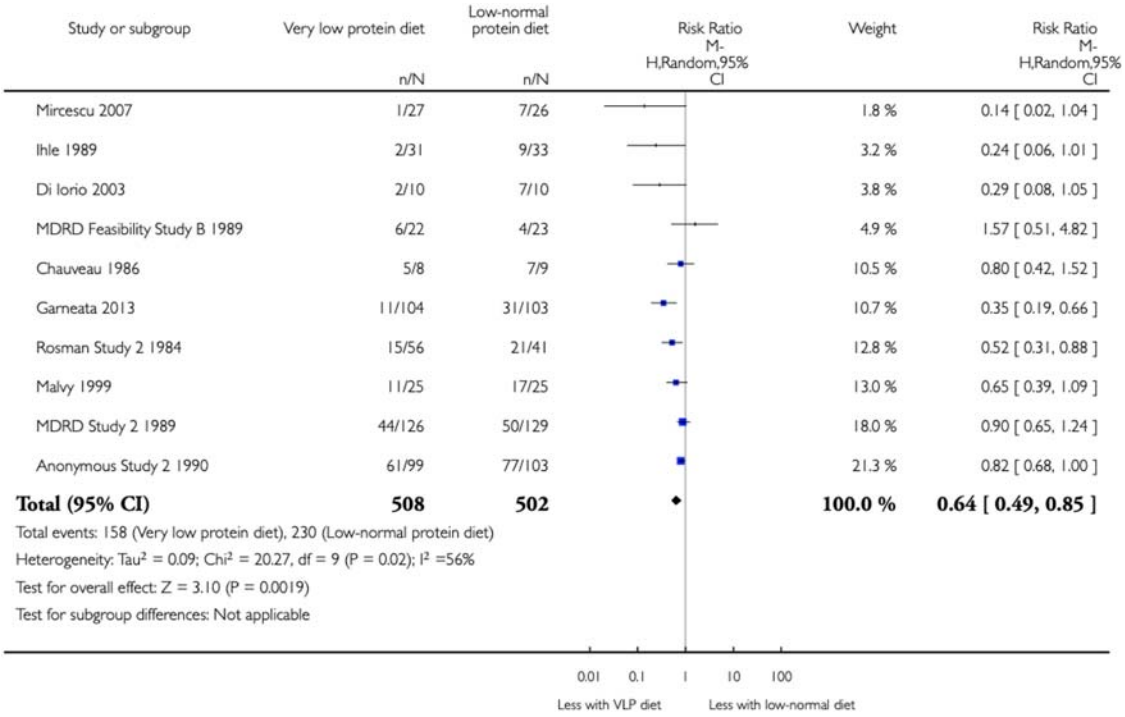
Metaanalysis is a comprehensive method aimed at searching, selecting, and analyzing appropriately designed clinical trials to increase the number of patients or observations and improve the power of statistical analysis [e.g., by reducing the confidence interval (CI)] [1,135,136]. To date, metaanalyses are considered to be second in validity of the evidence it provides, immediately behind the evidence provided by large randomized trials (considered to be level one), and equal to small randomized trials [137]. Three metaanalyses have been performed on low-protein diets [1,138–140]. These reports have searched the literature by different ways to ensure the most exhaustive collection of trials, including international databases in non-English languages. The most rigorous criteria for selecting or rejecting papers for analysis include consideration of randomized controlled trials only, since it is generally believed that nonrandomized controlled trials are more likely to give biased results than their randomized counterparts [140].

In an attempt to examine the impact of low-protein diets on loss of GFR, Kasiske and associates summarized a total of 24 controlled clinical trials, of which 13 were randomized [140]. The main outcome was the loss of GFR over time (mL/min/year) in groups receiving or not a low-protein diet. A total of 2248 patients were collected from which 1919 were enrolled in randomized studies. GFR loss was lower by 0.53 mL/min/year (95% CI, 0.08–0.98) in the lower protein intake group ($P < .05$).

Based on this background, we identified 17 randomized controlled trials, including 2996 patients suitable for analysis, among 133 reports of clinical trials assessing the effects of low-protein diets for the treatment of patients with chronic kidney insufficiency [1]. Gender and the nature of kidney disease were equally distributed in control and more restricted groups; thus these avoiding well-identified independent causes for more rapid progression of kidney disease would not influence the results.

In the low-protein intake subanalysis, there were 904 patients with a low-protein intake (0.5–0.6 g protein/kg/day) and 910 individuals with a normal protein intake. In the low-protein diet group, 130 dialysis starts were found, while 131 in the larger protein intake group, giving a nonsignificant odds ratio of 1.05, CI 0.73–1.53 ($P = \text{NS}$). In the very low-protein intake subanalysis, there were 508 patients with a very low-protein intake (0.3–0.4 g protein/kg/day) and 502 individuals with a low-normal protein intake (Fig. 16.11). In the VLPD group, 158 dialysis treatments were found, while 230 in the larger protein intake group, giving an odds ratio of 0.64, CI 0.49–0.85 ($P = .0019$, Fig. 16.11). This indicates that a very low protein diet resulted in a 36% reduction for starting dialysis as compared with larger or unlimited protein intakes [1]. It also suggests that a moderately reduced protein intake may not be protective enough and a better metabolic control may be obtained by a very low protein diet, thus postponing the need for dialysis. Interestingly, it should be noted that the nutritional status of patients was also assessed. Body weight changes were pooled as well as protein energy wasting and no signs of weight loss ($n = 514$ patients) or declared protein energy wasting ($n = 2373$ patients) were reported in patients whose nutritional data were available [1].

In patients with diabetes and kidney disease (DKD), the situation is less clear. Previous guidelines recommended a protein intake of 0.8 g/kg body weight/day in patients with CKD stages 1–5. However, the KDIGO guidelines suggested more liberalization with protein restriction and recommended that 0.8 g/kg body weight/day be maintained and avoiding levels above 1.3 g/kg/body weight. Ko et al. conducted an extensive review of existing guidelines and original research in patients with DKD and indicated that a dietary protein intake of 0.8 g/kg body weight/day was advised for DKD not on dialysis [141]. However, due to the fact that uremic toxins accumulate in DKD patients as well and may increase insulin resistance, and these patients do not have increased protein



Study or subgroup	Very low protein diet n/N	Low-normal protein diet n/N	Weight	Risk Ratio M-H,Random,95% CI
Mircescu 2007	1/27	7/26	1.8 %	0.14 [0.02, 1.04]
Ihle 1989	2/31	9/33	3.2 %	0.24 [0.06, 1.01]
Di Iorio 2003	2/10	7/10	3.8 %	0.29 [0.08, 1.05]
MDRD Feasibility Study B 1989	6/22	4/23	4.9 %	1.57 [0.51, 4.82]
Chauveau 1986	5/8	7/9	10.5 %	0.80 [0.42, 1.52]
Garneata 2013	11/104	31/103	10.7 %	0.35 [0.19, 0.66]
Rosman Study 2 1984	15/56	21/41	12.8 %	0.52 [0.31, 0.88]
Malvy 1999	11/25	17/25	13.0 %	0.65 [0.39, 1.09]
MDRD Study 2 1989	44/126	50/129	18.0 %	0.90 [0.65, 1.24]
Anonymous Study 2 1990	61/99	77/103	21.3 %	0.82 [0.68, 1.00]
Total (95% CI)	**508**	**502**	**100.0 %**	**0.64 [0.49, 0.85]**

Total events: 158 (Very low protein diet), 230 (Low-normal protein diet)

Heterogeneity: $Tau^2 = 0.09$; $Chi^2 = 20.27$, df = 9 (P = 0.02); $I^2 = 56\%$

Test for overall effect: Z = 3.10 (P = 0.0019)

Test for subgroup differences: Not applicable

FIGURE 16.11 A systematic review of the results from randomized controlled studies of the influence of very low protein diets in delaying the start of maintenance dialysis. A square denotes the odds ratio (treatment/control) for starting dialysis for each trial, and the diamond indicates the combined results of all trials; 95% CIs are represented by horizontal lines. Studies included a very low-protein intake (0.3–0.4 g protein/kg/day) compared to a greater amount of dietary protein (0.5–0.6 g protein/kg/day or a free diet). Overall, the "common" odds ratio = 0.64 (95% CI: 0.49, 0.85), *P* = .0019. *CI*, Confidence interval. Source*: From Hahn D, Hodson EM, Fouque D. Low protein diets for non-diabetic adults with chronic kidney disease. Cochrane Database Syst Rev 2018;10:CD001892 with permission.*

BOX 16.1

AND-KDOQI energy and protein requirements [97]

Energy intake In adults with CKD 1–5D (1C) who are metabolically stable, we recommend prescribing an energy intake of 25–35 kcal/kg/day based on age, gender, level of physical activity, body composition, weight status goals, KD stage, and concurrent illness or the presence of inflammation to maintain normal nutritional status.

Protein restriction, nondialysis, nondiabetic. In adults with CKD 3–5 who are metabolically stable, we recommend, under close clinical supervision, protein restriction with or without ketoacid analogs, to reduce risk for ESRD/death (1A) and improve QoL (quality of life) (2C).

- a low-protein diet providing 0.55–0.60 g dietary protein/kg ideal body weight/day, OR;
- a VLPD providing 0.28–0.43 g dietary protein/kg ideal body weight/day with additional ketoacid/amino acid analogs to meet protein requirements (0.55–0.60 g/kg body weight/day).

Protein restriction, nondialysis, diabetic. In the adult with CKD 3–5 and who have diabetes, it is reasonable to prescribe, under close clinical supervision, a dietary protein intake of 0.6–0.8 g/kg ideal body weight per day to maintain a stable nutritional status and optimize glycemic control (OPINION).

needs, the recent AND-KDOQI guideline advised for a protein intake of 0.6–0.8 g/kg/day [97] (Box 16.1).

Finally, the number needed to treat (NNT), a methodological tool, is routinely used to compare the efficacy of a given treatment in different studies [142]. It theoretically represents the number of patients that must be treated by a given intervention to avoid one extra death or a prespecified event per year. From the previous metaanalysis data [138], NNT conferred by a low-protein intervention stands between 2 and 56, depending on the study. For example, NNT was estimated to be 4 in the most recent Garneata study [143], a very low number that favorably compares with the well-accepted mortality reduction obtained by statins in the 4S trial (NNT = 30) and WOSCOPS study (NNT = 111) [144]. This analysis gives further support to the thesis that dietary protein restriction is an effective therapeutic intervention.

Conclusion

Many experimental studies provide evidence for the beneficial effects of low-protein intakes. These benefits include reduction in uremic toxicity, healthier nutritional status, particularly if energy intake is well maintained, reduced proteinuria and slowing of the loss of kidney function and finally delay the need for kidney replacement therapy. These results have been observed with a fairly good level of evidence in large clinical trials, systematic reviews, and guidelines, all recently updated [1,97,134,145]. Such low-protein diets, of course, do not prevent the loss of kidney function in patients with rapidly progressive kidney disease. Thus in all other patients with CKD, it may be worth prescribing a reduction in dietary protein intake.

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C H A P T E R

17

Disorders of phosphorus homeostasis: emerging targets for slowing progression of chronic kidney disease

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Introduction

Rates of cardiovascular disease events and death increase in a linear fashion as kidney function declines [1,2]. This supports an emphasis on uncovering potentially modifiable risk factors for kidney disease progression in individuals with early stages of chronic kidney disease (CKD) in the hopes that slowing progression will improve long-term outcomes. To date, however, relatively few factors have emerged as effective targets for slowing the progression of CKD, representing an important unmet need in nephrology research.

High serum phosphorus concentrations are an established risk factor for cardiovascular disease events and death, particularly among individuals with CKD [3–6]. Although the mechanisms for these associations remain incompletely understood, a considerable body of evidence suggests a direct causal relationship between higher serum phosphorus concentrations and cardiovascular disease [7–12]. In addition, excess phosphorus stimulates the secretion of hormonal regulators of phosphorus metabolism such as parathyroid hormone (PTH) and fibroblast growth factor 23 (FGF23) [13–15], elevated circulating concentrations of which have emerged as robust risk factors for cardiovascular disease events and mortality [3,16–18]. Phosphorus excess has been implicated in the pathogenesis of kidney injury via similar mechanisms [19–37], suggesting that disorders of phosphorus metabolism may be promising therapeutic targets for attenuating kidney function decline in CKD patients. Since excess dietary phosphorus intake plays a central role in the pathogenesis of disordered phosphorus homeostasis in CKD, these findings have fueled renewed interest in restricting dietary phosphorus consumption and intestinal phosphorus absorption as a potential therapy for preserving residual kidney function in CKD patients. The focus of the current section will be to review the evidence both supporting and refuting this possibility, critically appraise current recommendations for restricting phosphorus intake in CKD, and consider the next steps required to establish the efficacy and feasibility of dietary phosphorus restriction for the preservation of kidney function in CKD patients.

Role of dietary phosphorus intake in disturbances of mineral metabolism in CKD

Serum phosphorus concentrations represent a highly dynamic balance between dietary phosphorus absorption, urinary phosphorus excretion, and exchanges with bone, soft tissue, and intracellular stores [38]. The kidneys are the primary organs that regulate this balance by modulating urinary phosphorus excretion in response to changes in diet intake and bone/soft tissue turnover. Under normal conditions, diet intake makes up the majority of the obligate phosphorus load

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(1200–1500 mg/day in a typical westernized diet) that the kidneys must eliminate on a daily basis to maintain phosphorus balance [39]. As such, dietary phosphorus absorption is the primary target of therapeutic interventions aimed at mitigating the development of hyperphosphatemia in patients with CKD.

Dietary phosphorus is well absorbed across the entirety of the intestinal tract by a combination of passive paracellular diffusion and active transport across luminal sodium–phosphorus cotransporters type II (Npt2b) and type III (Pit1) [40]. Although passive diffusion in the duodenum and jejunum appears to be the primary route of dietary phosphorus absorption, studies in Npt2b knockout mice revealed that sodium-dependent active transport may account for as much as 45%–50% of total intestinal phosphorus transport [41]. 1,25-Dihydroxyvitamin D ($1,25(OH)_2D$) enhances active intestinal phosphorus absorption by stimulating Npt2b expression [42]. However, unlike its role with calcium, $1,25(OH)_2D$ is not essential for the absorption of phosphorus from the intestinal lumen since passive paracellular routes of diffusion allow for substantial dietary phosphorus absorption even in settings of profound $1,25(OH)_2D$ deficiency [40].

Most circulating inorganic phosphorus is freely filtered in the renal glomeruli and enters renal proximal tubules. Under typical dietary conditions, 80%–90% of the filtered load is reabsorbed across sodium–phosphorus cotransporters 2a and 2c (Npt2a and Npt2c) in proximal tubular cells (as well as other minor transporters), and the rest is excreted in the urine [43]. PTH and FGF23 are the primary hormones that regulate the fraction of filtered phosphorus that is reabsorbed in renal proximal tubules. Both the hormones do so by downregulating sodium–phosphorus cotransporters in renal proximal tubule cells, thereby decreasing tubular phosphorus reabsorption and augmenting urinary phosphorus excretion [39,44]. In addition, FGF23 limits dietary phosphorus absorption by lowering $1,25(OH)_2D$ concentrations via the inhibition of 25-hydroxyvitamin D-1α-hydroxylase, which converts 25(OH)D to $1,25(OH)_2D$, and by the stimulation of 24-hydroxylase, the major catabolic pathway for $1,25(OH)_2D$ [44].

Increased phosphorus intake stimulates the secretion of PTH and FGF23, which mitigates hyperphosphatemia by enhancing urinary phosphorus excretion and, in the case of FGF23, by limiting dietary phosphorus absorption via lowering $1,25(OH)_2D$ levels [13–15]. This appears to be particularly critical for maintaining phosphorus homeostasis in CKD patients in whom elevations in FGF23 and PTH play a key role in enhancing per-nephron urinary phosphorus excretion in the face of unrestricted phosphorus intake. A number of observations support this view. In a study of 404 patients with stage 3 or 4 CKD and secondary hyperparathyroidism randomized to either cinacalcet or placebo for 32 weeks, cinacalcet-treated patients had a 43% decrease in mean serum PTH concentrations but at the price of a 21% increase in mean serum phosphorus concentrations, due mainly to diminished urinary phosphorus excretion as a consequence of the decreased PTH [45]. Similarly, in a study of rats with experimentally induced kidney disease, intravenous injection of anti-FGF23 antibodies resulted in a decrease in urinary fractional excretion of phosphorus via lowering FGF23 levels and, consequently, a marked elevation in serum phosphorus [46], underscoring the critical importance of elevated FGF23 levels in the control of serum phosphorus in CKD. When these data are coupled with animal and human studies showing that the restriction of dietary phosphorus absorption decreased, and in some cases normalized, FGF23 and PTH levels in CKD [47–57], these findings support the concept that dietary phosphorus intake plays a pivotal role in the pathogenesis of disordered phosphorus metabolism in CKD.

Disorders of phosphorus homeostasis and kidney disease progression

Phosphorus excess has long been implicated in the pathogenesis of kidney disease through a variety of proposed mechanisms (Table 17.1). In a series of experiments conducted in the 1930s, rats fed with normal kidney function diets containing markedly high amounts of inorganic phosphorus (ranging from 2% to 6.5%) for about 6 weeks developed renal tubular necrosis, diffused renal parenchymal calcification, inflammation, and associated interstitial fibrosis [58]. These effects appeared to be accentuated in the setting of kidney disease. In a classic study published by Ibels and colleagues in 1978, two groups of rats underwent subtotal nephrectomy to induce chronic uremia, after which they were fed a diet containing either a standard amount of phosphorus (0.5%) or a low-phosphorus content (0.04%) plus aluminum hydroxide for a total of 6 weeks [27]. Importantly, both diets contained similar amounts of protein. While mean serum creatinine concentrations increased to a similar degree in both groups of rats 4 weeks after the induction of kidney disease, creatinine concentrations continued to increase afterwards in the rats placed on a standard phosphorus diet, whereas they remained stable in rats placed on a phosphorus-depleted diet. In addition, all 26 animals placed on the standard phosphorus diet died prior to the end of the 6-week experimental period, whereas only 3 of the 12 animals fed the phosphorus-restricted

TABLE 17.1 Proposed mechanisms underlying a link between excess dietary phosphorus intake or serum phosphorus concentrations and kidney disease progression.

Mechanisms	Comments
Precipitation of calcium–phosphorus microcrystals into renal parenchyma	Most common pattern of injury noted in animals fed with high-phosphorus diets; induces interstitial fibrosis, tubular atrophy, and proteinuria [25–27,29,31,33]
Stimulation of phosphaturic hormones, such as parathyroid hormone and fibroblast growth factor 23	Higher concentrations of parathyroid hormone have been associated with increased cytosolic-free calcium in renal tubules [30]; higher fibroblast growth factor 23 concentrations have been independently associated with faster kidney disease progression in observational studies [17,18,24,59]
Promotion of vascular calcification	High-phosphorus intake and excess serum phosphorus concentrations have been linked to vascular calcification in the aorta, major branch vessels, and peritubular and capillary vessels within the kidneys [26,27,31]
Stimulation of inflammatory pathways	Inflammation has been causally implicated in the nephrotoxicity of excess phosphorus intake in animal models of immune-mediated glomerulonephritis [28]

diet died. Histological examination of kidney tissue obtained ex vivo revealed significantly higher calcium and phosphorus content and interstitial fibrosis in kidneys from rats fed with the standard phosphorus diet as compared to the phosphorus-depleted diets, consistent with a direct pathological effect of excess phosphorus load on renal parenchyma.

Subsequent studies showed very similar findings in other rat models of kidney disease [26,28,29,31], and in studies using oral phosphorus binders instead of dietary phosphorus reduction as the primary method of limiting intestinal phosphorus absorption [33]. High-phosphorus consumption has also been shown to have deleterious effects on kidney function in companion animals, such as dogs and cats [22,23,60]. In cats with normal kidney function, very high-phosphorus consumption (five-times above maintenance requirements) resulted in higher levels of urinary albumin excretion and glycosuria as compared to cats maintained on normal phosphorus consumption [61]. In line with these findings, lower phosphorus intake lowered the degree of kidney calcification in growing kittens at the cost of a slight decrease in weight gain and in tibia length [62] and reduced the development of urolithiasis in healthy adult cats [63]. These findings may be particularly important for cats, which have a relatively high incidence of CKD [64], in part, due to the development of nephrocalcinosis with aging [65]. Reduction in phosphorus consumption was also shown to reduce kidney calcification in rabbits without compromising normal growth patterns [66]. Dietary phosphorus restriction appears to be particularly beneficial in companion animals with kidney disease. Lower phosphorus consumption slows kidney disease progression in both dogs and cats with established kidney disease and also seems to prolong survival [22,23,60]. Notably, a number of these studies showed that animals fed with phosphorus-restricted diets had slower kidney disease progression than animals fed with phosphorus-replete diets despite no differences in the intake of protein or other nutrients [23,27,28,31], indicating that phosphorus restriction may have salutary effects on kidney function preservation independent of the known beneficial effects of protein restriction [67].

Although the impact of phosphorus excess on CKD progression in humans has been examined in less detail, some data suggest that phosphorus overload contributes to kidney function decline. Large observational studies showed that higher serum phosphorus concentrations were associated with faster kidney disease progression and higher risk of incident end-stage kidney disease (ESKD) independently of such established risk factors as lower baseline–estimated glomerular filtration rate (eGFR) [21,34–37]. Increased plasma FGF23—a marker of phosphorus overload—has also been shown to be a robust risk factor for kidney disease progression in CKD patients, as depicted in Fig. 17.1 showing the direct association between FGF23 and CKD progression in individuals with advanced CKD [17,18,24,59]. Even among individuals with normal kidney function and serum phosphorus concentrations within the normal range, a higher serum phosphorus level at baseline was independently associated with higher risk of incident CKD [35]. This suggests that excess serum phosphorus may impair renal health at all levels of kidney function.

Observational studies examining the relationship between dietary phosphorus consumption, and kidney disease progression are much fewer in number, in large part because of limitations in estimating phosphorus consumption using standard dietary instruments. Nonetheless, to try to overcome this limitation, several studies used urinary phosphorus excretion as a proxy for dietary phosphorus consumption. In an

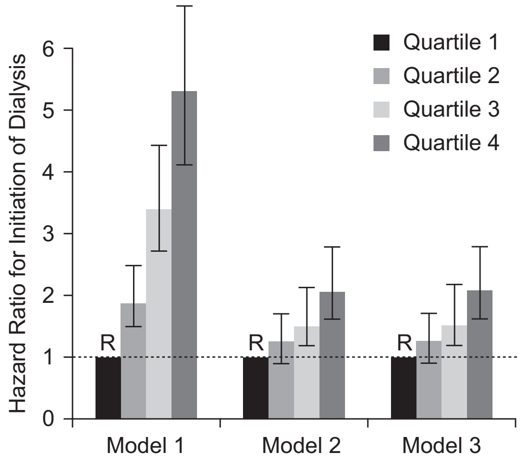

FIGURE 17.1 Hazard ratio (95% CI) for the progression of kidney disease as indicated by the initiation of chronic hemodialysis in patients with advanced chronic kidney disease according to quartiles of fibroblast growth factor 23 at baseline. Model 1 was adjusted for age, gender, and race. Model 2 was adjusted for variables in Model 1 plus smoking, alcohol intake, diabetes, hypertension, prevalent cardiovascular disease, Charlson score, body mass index, systolic and diastolic blood pressure, homocysteine, folate, vitamin B_{12}, treatment arm, hemoglobin, estimated glomerular filtration rate, albumin, calcium, phosphorus, 25-hydoxyvitamin D, 1,25-dihydroxyvitamin D, intact parathyroid hormone, total cholesterol, LDL-cholesterol, HDL-cholesterol, and triglycerides. Model 3 adjusted for variables in Model 2 plus medications. Quartile 1 is the referent group in all models. *CI*, Confidence interval; *HDL*, high-density lipoprotein; *LDL*, low-density lipoprotein. *From Kendrick J, Cheung AK, Kaufman JS et al. FGF-23 associates with death, cardiovascular events, and initiation of chronic dialysis. J Am Soc Nephrol 2011;22:1913–22.*

analysis of 795 participants of the modified diet in renal disease study, Selamet et al. found no statistically significant associations of urinary phosphorus excretion (from 24-hour urine collections at baseline) with the development of ESKD over an average of 16 years of follow-up [68]. In a retrospective cohort study of 175 Japanese CKD patients who were hospitalized and placed on a low-protein diet, higher 24-hour urinary phosphorus/creatinine clearance ratios at baseline were associated with higher risk of CKD progression (i.e., the development of a 50% decline in eGFR or ESKD) independently of other risk factors over about 1.5 years of follow-up [69]. However, 24-hour urine collections in this latter study were obtained while patients were hospitalized and after they were placed on a low-protein diet. So the urine measurements most likely did not reflect ambient dietary phosphorus consumption at home after discharge. Furthermore, a study of CKD patients who underwent detailed balance studies to examine the effects of calcium-based phosphorus binders on total-body phosphorus balance showed that urinary phosphorus excretion was more closely associated with total-body phosphorus retention than dietary phosphorus consumption, indicating that 24-hour urinary phosphorus excretion may not be a good proxy for dietary phosphorus consumption in CKD patients [70]. In aggregate the balance of data from observational studies does not demonstrate a clear association of dietary phosphorus intake with CKD progression.

There are few prospective trials testing whether reducing dietary y phosphorus attenuates CKD progression, and the results remain unclear. Nevertheless, a number of studies have shown that dietary protein restriction may help slow kidney disease progression in CKD patients, as reviewed elsewhere in this text. Since dietary phosphorus is closely linked to protein intake, it is possible that concomitant reductions in phosphorus intake may have contributed to the beneficial effect of protein restriction. Several small human studies support this possibility. Maschio et al. showed that the progression of kidney disease (as assessed by increases in the reciprocal of serum creatinine) was significantly slower in three groups of patients assigned to low-phosphorus diets (600–750 mg/day) (total $n = 53$) than in a fourth group of patients ($n = 30$) consuming an unrestricted diet estimated to provide 900 mg of phosphorus per day [32,71]. Interestingly, the magnitude of change in the reciprocal of serum creatinine with phosphorus restriction in this study was inversely related to baseline kidney function [32], suggesting that dietary phosphorus restriction is most beneficial when implemented in early CKD. In a study of 39 CKD patients, Barsotti et al. showed that reducing phosphorus intake (to 7 mg/kg/day) in CKD patients already consuming low-nitrogen (protein) diets was more effective in preserving kidney function than consuming a low-nitrogen diet with higher amounts of phosphorus (12 mg/kg/day) over about 1 year of follow-up [20]. In a subsequent study by the same group, 55 patients with moderate CKD (mean creatinine clearance, 30 mL/min) were followed on ad libitum diets for about 12 months after which they were assigned to a low-phosphorus (6.5 mg/kg/day), low-nitrogen diet for an average of 21 months ($n = 29$), or a conventional low-nitrogen diet providing 12 mg phosphorus/kg/day of phosphorus per day for about 17 months ($n = 26$) [19]. Creatinine clearance rates in both groups were noted to decline at an equal rate while the patients were consuming ad libitum diets. The creatinine clearance stabilized in the group assigned to the low-phosphorus, low-nitrogen diet, whereas it continued to decline in the conventional low-nitrogen diet group. The authors interpreted these data to suggest that a low-phosphorus diet confers a benefit on kidney disease progression above and beyond low protein intake in patients with moderate CKD.

While intriguing, these studies have a number of critical limitations that should merit caution when interpreting the results. First, they did not consistently isolate the effects of phosphorus restriction from the potential beneficial effects of other interventions, such as protein restriction and/or more intensive medical care due to frequent study visits. This makes it unclear whether dietary phosphorus restriction per se was the primary beneficial intervention [30]. In addition, the number of patients studied was very small; the intervention periods were relatively short; contemporaneous, well-matched controls were not used; and changes in serum creatinine or creatinine clearance over time were not corrected for any changes in muscle mass owing to decreased protein intake. Furthermore, not all studies report beneficial effects of dietary phosphorus restriction, and two small studies showed no effect of phosphorus restriction on kidney disease progression in CKD patients [72,73].

Due to these limitations, at present there is no good-quality evidence in humans that supports the use of dietary phosphorus restriction to preserve kidney function in CKD patients. Randomized controlled trials formally testing whether dietary phosphorus restriction attenuates kidney disease progression in predialysis CKD patients are now needed, particularly in light of the encouraging animal and human data reviewed earlier.

Dietary phosphorus restriction in CKD: practical considerations moving forward

Despite the lack of randomized controlled trials supporting its efficacy, restricting dietary phosphorus intake has been advocated for the management of disturbances in bone and mineral metabolism in CKD since the 1970s [57,74]. These recommendations were based upon animal and human studies showing that even modest reductions in phosphorus intake lowered PTH concentrations, attenuated parathyroid gland hyperplasia, and ameliorated high-turnover bone disease, particularly in early CKD [47–49,51,56,75]. More recently, therapy with noncalcium-based oral phosphorus binders and consumption of vegetable sources of phosphorus with low bioavailability were shown to decrease plasma FGF23 concentrations in CKD patients [50,53–55], further supporting the utility of restricting dietary phosphorus absorption in CKD. To date, however, the utilization of dietary phosphorus restriction in clinical practice has been limited by a number of practical issues, many of which will need to be addressed in the design of any future clinical trials assessing the efficacy of phosphorus restriction in slowing CKD progression.

First, the optimal timing of dietary phosphorus restriction in CKD patients needs to be more clearly defined. Current clinical practice guidelines are available from the National Kidney Foundation Kidney Disease Outcome Quality Initiative (KDOQI) and the Kidney Disease Improving Global Outcomes (KDIGO) Study Group [76,77]. Both sets of guidelines essentially advocate prescribing dietary phosphorus restriction to avoid biochemical evidence of phosphorus overload, defined either as hyperphosphatemia or elevations of PTH above stage-specific threshold levels. The guidelines contain subtle differences as to when to initiate therapy. The KDOQI guidelines recommend adjusting dietary phosphorus intake to maintain serum phosphorus concentrations within the normal range. In contrast the KDIGO guidelines do not support initiating therapy until serum phosphorus concentrations are frankly elevated, discouraging intervention in individuals with normal serum phosphorus concentrations. This latter approach is perhaps reasonable given the lack of clinical trial data showing that lowering dietary phosphorus absorption (either through lower phosphorus intake or the use of oral phosphorus binders) improves clinical outcomes. However, waiting for the evidence of phosphorus overload to manifest prior to instituting dietary phosphorus limitation may miss an important opportunity to ameliorate kidney injury in early CKD. Indeed, studies showed that rats with experimentally induced kidney disease fed with high-phosphorus diets developed extensive renal parenchymal damage even in the absence of significant increases in serum phosphorus [26,67]. Furthermore, CKD patients prescribed low-phosphorus diets—manifested stabilization of kidney function even though their serum phosphorus concentrations were well within the normal range throughout the study period [19,32]. While these data suggest that implementing dietary phosphorus restriction in mild-to-moderate stages of CKD may help to protect residual renal function, even in the absence of overt evidence of phosphorus excess, it is unclear exactly how early during the course of kidney disease dietary phosphorus restriction should be implemented to maximize these potential benefits. This will require further study.

Further complicating this issue is the lack of evidenced-based recommendations for the degree of dietary phosphorus restriction that should be prescribed in individual patients. Although older KDOQI guidelines suggest phosphorus restriction to 800–1000 mg/day in stage 3–5 CKD patients with hyperphosphatemia or elevated PTH levels, there exist few data to support this recommendation. Further, it seems unlikely that one target range would be suitable for such a wide spectrum of kidney disease severity. Indeed, animal studies have shown that as renal function is reduced, the nephrotoxicity of excess phosphorus is greatly enhanced [26,27], so that progressively smaller quantities of phosphorus intake are needed to induce kidney injury at lower levels of kidney function. Consistent with this finding, reductions in phosphorus intake that were proportional to concurrent reductions in glomerular filtration rate were shown to be necessary for maintaining normal serum phosphorus and PTH concentrations in canine models of CKD [56]. Whether similar CKD stage-specific, proportional decreases in phosphorus intake are more appropriate for the treatment of disorders of mineral metabolism and preservation of kidney function than a single target range has not been well studied in humans and remains unclear. Addressing this issue will be critical for developing rational recommendations for dietary phosphorus restriction in patients across the spectrum of kidney disease.

In addition, appropriate targets for gauging the efficacy of therapy are needed. While serum phosphorus concentrations would seem to be natural candidates, population-based data showed that even small decreases in serum phosphorus (~0.3–1.0 mg/dL) within the normal range were associated with decreased risks of adverse outcomes, including cardiovascular disease, progression of kidney disease, and death [4–6,35,36,78]. Targeting such small changes in serum phosphorus to gage the efficacy of phosphorus reduction strategies in individual predialysis CKD patients would be unrealistic in a clinical trial, much less in clinical practice. This is especially the case given the wide daily fluctuations in serum phosphorus concentrations due to natural postprandial or diurnal variation [79]. Further, studies in CKD patients have shown that serum phosphorus concentrations are minimally responsive to decreases in dietary phosphorus absorption unless intake is severely restricted. FGF23 has been proposed as a more appropriate biomarker to gauge the efficacy of phosphorus reduction strategies given that plasma FGF23 concentrations manifest much less random variation [80]. In support of this, modest restrictions in dietary phosphorus consumption produce measurable decreases in FGF23 and PTH, suggesting that these markers may be better integrated ones of phosphorus responsiveness. In addition, since elevations in plasma FGF23 are among the earliest manifestations of disordered phosphorus metabolism in CKD [81], FGF23 could also potentially serve as a biomarker to help identify early-stage CKD patients with normal serum phosphorus and PTH levels who may nevertheless benefit from dietary phosphorus restriction in order to maintain phosphorus balance. Future studies will need to test this possibility and determine the most appropriate targets for assessing the efficacy of phosphorus restriction in individual patients.

Finally, given the close relationship between dietary phosphorus and protein, reasonable concerns have been raised that restricting phosphorus intake would require a reciprocal restriction in protein intake that could exacerbate protein-energy wasting in advanced CKD [82]. As such, practical strategies for safely restricting phosphorus intake in the outpatient setting need to be better defined. Importantly, numerous strategies have already been proposed, with most involving a shift in the focus of dietary phosphorus management from globally reducing phosphorus (and thus, protein) intake to optimizing the types and sources of phosphorus being consumed [83]. Such strategies include decreasing the consumption of processed foods containing high quantities of phosphorus-based food additives, consuming more vegetable-based protein sources with lower phosphorus bioavailability, or increasing the consumption of foods with low phosphorus-to-protein ratios [83]. Before dietary phosphorus restriction can be broadly adopted in the management of patients with predialysis CKD, these and the other barriers reviewed earlier will need to be addressed.

Conclusion

Disorders of phosphorus metabolism are strongly linked to adverse CKD outcomes, including CKD progression. Given the central role of dietary phosphorus intake in the pathogenesis of disturbances of phosphorus homeostasis in CKD, restriction of dietary phosphorus consumption may represent an effective intervention for mitigating the decline of kidney function in CKD patients. While the balance of experimental and human data supports this thesis, the lack of randomized, controlled trials examining the utility and/or feasibility of this intervention precludes the ability to recommend dietary phosphorus restriction for the attenuation of CKD progression at this time. As the phosphorus content of westernized diets will only increase in the future, initiating these trials should be a high priority, with the long-term goal of determining whether dietary phosphorus intake may be an effective and safe therapy for slowing the progression of CKD.

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C H A P T E R

18

Therapeutic strategies to limit tryptophan metabolites toxicity during chronic kidney disease

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Introduction: Gut-derived uremic toxins

Numerous uremic retention solutes (URS) that would normally be cleared by the kidneys accumulate in chronic kidney disease (CKD). These solutes are called uremic toxins when they interact negatively with biological functions. Many studies have shed light on the URS production mechanisms, and a classification of URS has been proposed according to their origin: (1) endogenous metabolism; (2) intestinal microbial metabolism, and (3) exogenous intake.

Studies with axenic mice or CKD patients undergoing a colectomy have helped to characterize the origin of URS [1,2]. In particular, using a spectrometry-based approach in these models, 11 major URS were identified as being microbiota-derived uremic solutes, including tryptophan (TRP) metabolites such as indoxyl sulfate (IS) and indole-3-acetic acid (IAA). IS and IAA have been almost consistently associated with increased mortality in CKD patients [3–7]. TRP metabolites, notably IS and IAA, are the most representative gut-derived uremic toxins and have emerged as an important therapeutic target.

Metabolism of tryptophan and indole production

TRP is an essential amino acid only supplied by dietary proteins composed of a β-carbon connected to the 3-position in an indole group (Fig. 18.1). Dietary TRP is metabolized via three pathways in the gastrointestinal tract, leading to kynurenine (KYN), indole, and serotonin derivatives [8].

The KYN pathway is the main metabolic route (95%) of TRP catabolism and is mediated by the enzymes tryptophan 2,3-dioxygenase and indoleamine 2,3-dioxygenase (IDO) in both immune and epithelial cells in the intestinal tract. Various metabolites can derive from the KYN pathway: 3-hydroxyanthranilic acid, 3-hydroxykynurenine (3-HKYN), kynurenic acid (KYNA), anthranilic acid, and quinolinic acid. The KYN pathway is well-balanced under physiological conditions but upregulated in several chronic diseases such as cancer and neurodegenerative disorders [9]. The accumulation of KYN metabolites has been less studied during CKD. Their plasma levels do not rise proportionally to the reduction in renal function because KYN is not a metabolic end product that is normally excreted by the kidney [10]. KYN levels seem increased in CKD patients [11] but this was not confirmed in all studies [12]. The mechanisms that explain a high level of KYN in CKD is not clear. IDO activity increases with the CKD severity and some data suggest that the induction of IDO may be a consequence of chronic inflammation [13]. Alternatively, renal insufficiency could impair the conversion of KYN to one of its downstream metabolites but this mechanism is unclear [10].

The gut microbial fermentation of dietary TRP is the main source of indole production. Indole is directly formed by intestinal bacteria expressing tryptophanase (e.g., *Lactobacillus*, *Bifidobacterium longum*, *Bacteroides*

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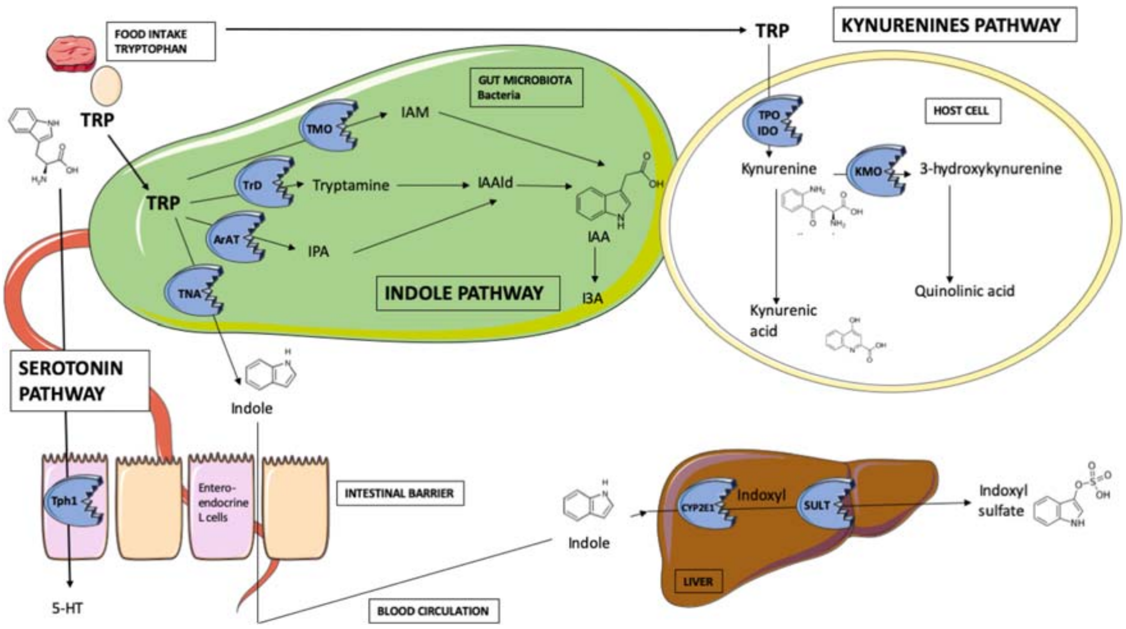

FIGURE 18.1 Overview of different pathways of tryptophan metabolites generation in human gut and endogenous production. *5-HT*, 5-Hydroxytryptamine; *ArAT*, aromatic amino acid aminotransferase; *CYP2E1*, p450 cytochrome CYP2E1 enzyme; *I3A*, indole-3-aldehyde; *IAA*, indole-3-acetic acid; *IAAld*, indole-3-acetaldehyde; *IAM*, indole-3-acetamide; *IDO*, indoleamine 2,3-dioxygenase; *IPA*, indole-3-propionic acid; *KMO*, kynurenine-3-mono-oxygenase; *SULT*, sulfatase; *TDO*, tryptophan 2,3-dioxygenase; *TMO*, tryptophan monooxygenase; *TNA*, tryptophanase; *Tph1*, tryptophan hydroxylase 1; *TrD*, Tryptophan decarboyxlase; *TRP*, tryptophan.

fragilis, *Parabacteroides distasonis*, *Clostridium bartlettii*, and *Eubacterium hallii*) [14]. Bacteria like *Lactobacillus* spp. convert TRP into IAA and indole-3-aldehyde through the tryptophan monooxygenase (TMO) [15]. IAA can also be produced endogenously via tryptamine catabolism by the tryptophan decarboxylase [16]. Bacteria like *Clostridium sporogenes* convert TRP into indole-3-propionic acid (IPA) via aromatic amino acid aminotransferase. After absorption from the intestinal tract into portal circulation, indole is first oxidized by the microsomal p450 cytochrome CYP2E1 enzyme and then converted into IS via the sulfatase enzyme (SULT1A1). Therefore, in CKD patients the gut microbial imbalance, called dysbiosis, is associated with an increased toxic metabolites generation, such as IS and IAA [17].

Under the catalytic action of tryptophan hydroxylase (Tph), TRP is degraded into 5-hydroxytryptamine (5-HT, called serotonin). Tph2 is expressed in neuronal cells. Tph1 catalyzes peripheral serotonin synthesis and is mainly expressed in the enterochromaffin cells of the gut. These cells are responsible for almost 90% of peripheral 5-HT synthesis. Additionally, a small amount of serotonin is synthesized in bone tissues. Several other metabolites are derived from this pathway such as 5-methoxytryptophan (5-MTP), 5-HIAA (5-hydroxyindoleacetic acid) or melatonin. Serum 5-HT and 5-HIAA increase during CKD whereas 5-MTP seems to decrease. So far, these metabolic changes have been poorly studied in CKD [18,19].

Tryptophan metabolites as aryl hydrocarbon receptor ligands

The aryl hydrocarbon receptor (AhR) is a ligand-activated transcription factor receptor and was discovered as a mediator of the toxic responses of halogenated and polycyclic aromatic hydrocarbons, such as dioxin (Fig. 18.2). Nevertheless, evidence accrued in the past years has shown that AhR is not only a receptor for xenobiotics but it can be activated by several endogenous ligands like TRP metabolites [20,21]. In CKD context, using microarray analyses of human umbilical vein endothelial cells (HUVECs), it has been shown that IS and IAA lead to an increased expression of AhR-induced genes [21]. The AhR is located in the cytoplasm of cells inside multiprotein complex (formed with stabilizer proteins, like heat shock protein 90, cochaperon p23 (P23), and X-associated protein 2. After ligand binding, AhR is activated by a conformational change that allows its translocation to the nucleus. After its phosphorylation by protein kinase C, the ligand-bound AhR complex is translocated into the nucleus. This ligand-bound AhR releases the multiprotein complex that binds to the AhR nuclear translocator

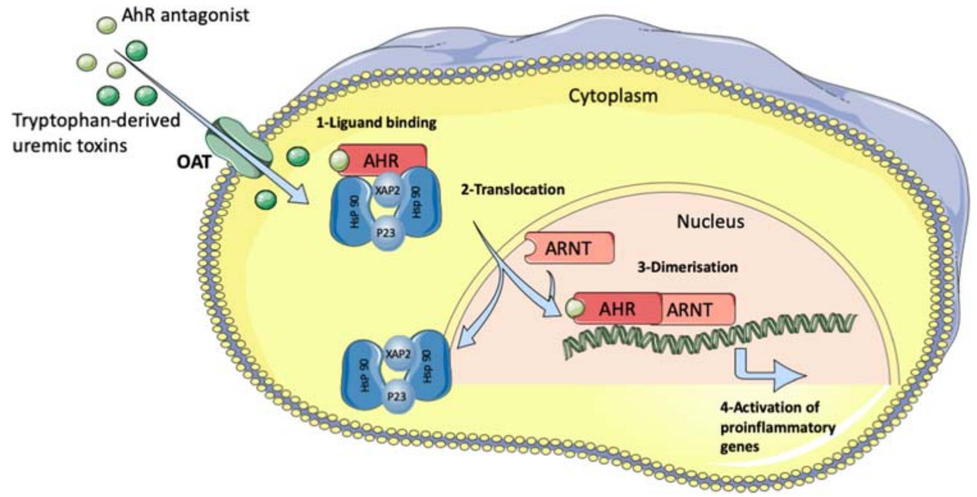

FIGURE 18.2 Mechanism of AhR activation by tryptophan-derived uremic toxins. *AhR*, Aryl hydrocarbon receptor; *ARNT*, AhR nuclear translocator; *HSP90*, heat shock protein 90; *OAT*, organic anion transporter; *XAP2*, X-associated protein 2.

(ARNT) through its PAS domain, resulting in the ligand-bound AhR-ARNT dimer. This dimer binds to specific DNA sequences (referred to as DRE or XRE for dioxin- or xenobiotic-responsive element) present in the promoter of wide genes, including cytochrome P450, family 1 member 1A (Cyp1A1); cytochrome P450, family 1, subfamily B (Cyp1B1); AhR repressor; and cyclooxygenase-2 (COX-2) [22].

The activation of AhR is first known to mediate the expression of drug metabolism enzymes but is also involved in diverse physiological functions such as the regulation of T-cell differentiation, conception and embryonic/fetal development, mediation of stress, and inflammation responses [23]. Although indoles and AhR activation in general appear to be beneficial, a large accumulation of TRP metabolites in CKD is associated with poor outcomes [3–7].

The classic AhR signaling is not able to explain all roles attributed to AhR. Thus a nongenomic inflammatory pathway of AhR activation may also be involved. The activation of transcription factors such as nuclear factor κB (NF-κB; which promotes the inflammatory response) and activator protein 1 (AP-1; which regulates target genes involved in cellular proliferation, transformation, and cell death functions) has also been described. The interaction between AhR and NF-κB can lead to activation or mutual transrepression of their activities, depending on the duration, the cell type used, and the promoter being assayed [24]. The cytosolic AhR can activate other cytosolic proteins, including proteins of the mitogen-activated protein kinase (MAPK) family, extracellular signal-regulated kinase (ERK), p38, and Jun-NH2-terminal kinase (JNK) [16]. MAPKs phosphorylate downstream transcription factors and thereby alter gene expression to direct a specific cellular response. These pathways were described in carcinogenesis processes, and their relevance in CKD complications has still to be demonstrated.

Tryptophan metabolites promote CKD progression

Several studies have demonstrated that TRP metabolic products are involved in CKD progression (Fig. 18.3) [25–27].

First, IS accelerates fibrosis by increasing the expression of transforming growth factor-beta, tissue inhibitor of metalloproteinase-1, intercellular adhesion molecule (ICAM-1 or CD-54), and procollagen I in cultured tubular cells [28–30]. In a porcine proximal tubular cell model, IAA reduced viable cell number, mainly through the induction of apoptosis. However, in this observation, IAA concentration was higher than that observed in CKD patients [31]. In cultured human renal tubular cells, IS reduced Klotho kidney expression through aberrant DNA methylation at the 5-position of cytosine in CpG dinucleotides in the Klotho gene [32]. This is of interest since a decrease in Klotho expression has been reportedly associated with kidney fibrosis. IS increased DNA methyltransferases 1, 3a, and 3b expression that are the key enzymes for the regulation of DNA methylation [32]. This suggests that epigenetic modifications by URS of specific genes may be an important pathophysiological mechanism for CKD progression [32].

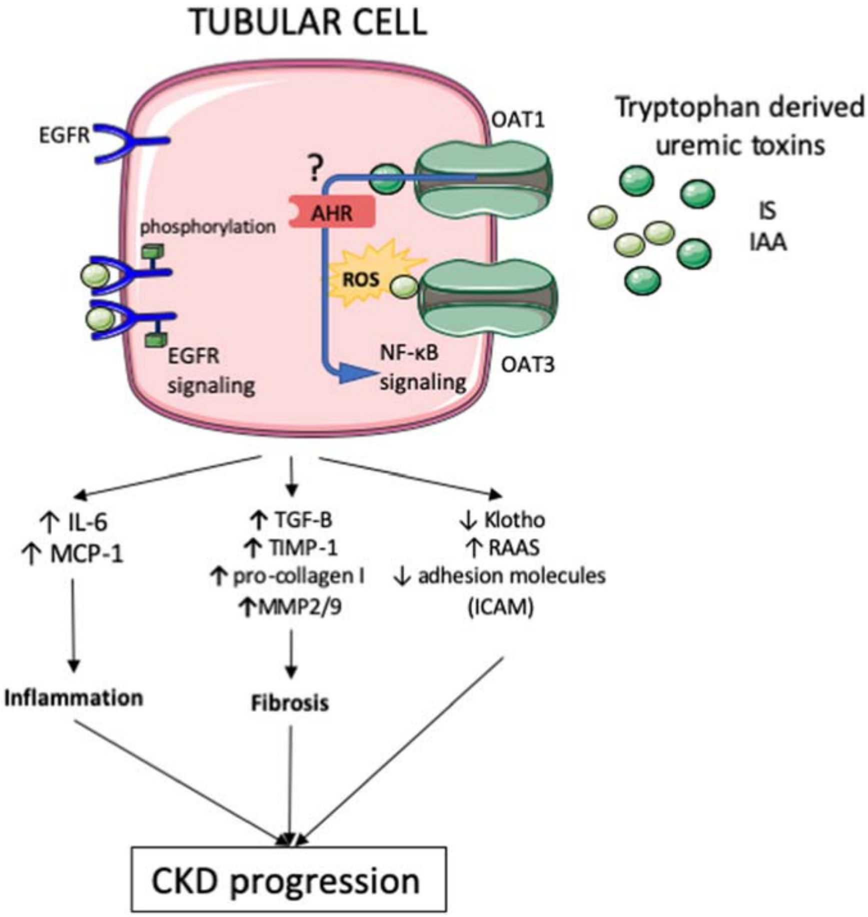

FIGURE 18.3 Mechanisms involved in nephrotoxicity of tryptophan-derived uremic toxins. *AhR*, Aryl hydrocarbon receptor; *CKD*, chronic kidney disease; *EGFR*, epidermal growth factor receptor; *IAA*, indole-3-acetic acid; *ICAM*, intercellular adhesion molecule; *IL-6*, interleukin 6; *IS*: indoxyl sulfate; *MCP-1*, monocyte chemoattractant protein 1; *MMP 2/9*, matrix metalloproteinases 2/9; *NF-κB*, nuclear factor κB; *OAT*, organic anion transporter; *RAAS*, renin–angiotensin–aldosterone system; *ROS*, reactive oxygen species; *TGF-β*, transforming growth factor-beta; *TIMP-1*, tissue inhibitor of metalloproteinase-1.

Second, IS accumulation in tubular cells lowers their antioxidative capacity [33,34] and increases the production of reactive oxygen species (ROS) [35]. IS is able to downregulate the renal expression of factor 2–related erythroid nuclear factor 2 (Nrf2) through the activation of NF-κB in human proximal tubular cells. Nrf2 controls antioxidant and antiinflammatory cellular responses by upregulating heme oxygenase-1 and NAD(P) H:quinone oxidoreductase 1 (NQO1). Also, IS inappropriately activated the renin–angiotensin–aldosterone system (RAAS) in proximal tubular cells, promoting kidney damage [36].

Third, IS markedly stimulates inflammation in tubular cells. Indeed, cultured mouse proximal renal tubular cells treated with IS increased their production of major proinflammatory cytokines such as interleukin 6 (IL-6) [27]. IS also injured podocytes by perturbing the actin cytoskeleton, decreasing the expression of podocyte-specific genes, and modulating the inflammatory response in cell culture [37].

The impact of IS on renal disease progression has been confirmed in virtually all animal studies. In CKD rats, the administration of IS accelerated glomerular sclerosis, fibrosis, and CKD progression [26,33,38]. IS administration in mice increased albuminuria by altering podocyte structure [37]. Decreasing IS accumulation in CKD rats by using the oral adsorbent AST-120 decreased tubular epithelial-to-mesenchymal transition [25]. In CKD rats, the oral intake of IAA at concentrations found in CKD patients resulted in a higher excretion of *N*-acetyl-β-glucosaminadase—a marker of tubular injury, an alteration of renal function, and a higher glomerular sclerosis index [39]. These findings are however not unanimous since in a recent study in CKD rats, administration of IS did not worsen renal impairment, and fibrosis and nonsignificant differences in Klotho mRNA expression were observed [40]. In a prospective CKD patients cohort, baseline IS was correlated with renal progression [41]. Further studies are therefore needed to explain these discrepancies.

On the contrary, on other intestinal TRP metabolites, IPA may be a renal protector against the development of CKD [42]. The putative protective effect of serum IPA may be explained by its antioxidative stress capacity, as IPA is a potent scavenger of hydroxyl radical [43].

The impact of kynurenine (KYN) metabolites on renal function has been less explored. KYN affects mesangial cell proliferation in culture [44]. More direct evidence for the effects of KYN metabolites on the progression of kidney disease has been revealed by studies using kynurenine-3-mono-oxygenase (KMO)-deficient mice, which catalyzes the hydroxylation of KYN to form 3-HKYN. Plasma levels of KYN and KYNA are higher in $KMO^{-/-}$ mice and a higher albuminuria and mild podocyte foot process effacement are observed [45].

Serotonin metabolites such as 5-MTP may have beneficial effect on renal function. 5-MTP attenuates the proinflammatory factor NF-κB and increases the antiinflammatory and antioxidant transcription factor Nrf2. In addition, treatment with 5-MTP in CKD mice significantly attenuated the upregulation of profibrotic proteins like collagene I, fibronectin, and E-cadherin [18].

Whether activation of AhR also accounts for some adverse effects on tubular cells and podocytes is still unknown. At least several actions of IS on proximal tubular cells, such as dysregulation of RAAS, are mediated by AhR [46]. A number of studies on adult mouse and human kidney have shown that AhR is localized in podocytes nuclei, as well as in distal tubules in human kidney. After exposure to IS, nuclear translocation of AhR was observed in cultured mouse podocytes [37].

Finally, AhR epidermal growth factor receptor (EGFR) activation by IS could contribute to renal tissue remodeling. Treatment of mice with IS significantly activated the renal EGFR and increased the tubulointerstitial expression of profibrotic proteins such as matrix metalloproteinases 2 and 9 [47]. The interaction between indole and EGFR needs to be confirmed.

Role of organic anion transporters in the nephrotoxicity of tryptophan metabolites

IS and IAA are secreted into the renal proximal tubule lumen by organic anion transporters (OATs) [48]. After IS exposure in rats, immunohistochemistry located IS in proximal and distal tubules, which express OAT1 (proximal tubules) and/or OAT3 (proximal and distal tubules) [33]. OAT1-knockout mice showed dramatically higher plasma concentrations of IS [49] and administration of the OAT inhibitor probenecid reduced IS toxicity in proximal tubular cells [33]. IAA is excreted in urine by tubular secretion through the OAT1 transporter [50]. Another tubular transporter, ATP-binding cassette transporter subfamily G member 2, has also been recently identified as an IS/IAA transporter [51].

Because several studies have suggested that the accumulation of TRP-metabolites accelerates tubular cell injury and acts as nephrotoxins, the preservation of renal residual function (RRF) is important. Different cohorts of hemodialysis patients have observed that plasma IS concentration is higher in anuric patients as compared with patients with conserved diuresis [52]. This gives some evidence that a reduction in TRP metabolites by RRF may be responsible for the benefits of observed association between RRF and mortality.

Tryptophan metabolites induce a vascular procoagulant phenotype and cardiovascular complications

Procoagulation state

CKD is associated with increased risk for thrombotic events (Fig. 18.4). Treatment of vascular smooth muscle cells (VSMCs) and peripheral blood mononuclear cells by IS or IAA at disease-relevant concentration increased their thrombogenicity. IS/IAA and KYN are able to upregulate tissue factor (TF) level by the AhR pathway, a major protein involved in the initiation of the coagulation process [53,54]. IS/IAA increased the stability of TF by inhibiting its ubiquitination [21,55]. Some studies suggest that IS promotes thrombosis with the ability to induce phosphatidylserine (PS) exposure and microparticles (MPs) release by red blood cells [56]. Externalized PS and MPs are binding sites for factor Xa and prothrombinase complexes. IS prompts to a ROS-induced p38MAPK signaling in platelets, triggering platelet hyperactivity that plays a crucial role in the uremic procoagulation state [57].

In good concordance, in mice exposed to IS, the weight of thrombus after laser-induced endothelial injury is increased [58]. Also, KYN enhances clotting after vascular injury in mice and regulates thrombosis in an AhR-dependent manner [54].

These experimental data have been confirmed in different cohorts of CKD patients. The concentration of circulating TF is positively correlated with plasma levels of IS and IAA [21]. KYN has been associated with serum markers of hypercoagulation in chronic dialysis patients [59]. Accumulations of IS, IAA, and KYN are independently associated with an increase of arteriovenous fistula thrombosis [54,60].

Inflammation state, oxidative stress, and endothelial dysfunction

Chronic inflammation and oxidative stress are key mechanisms during endothelial dysfunction and atherosclerosis. The correlation between IS/IAA accumulation and inflammatory markers such as monocyte chemoattractant protein 1 or IL-6 has been confirmed in clinical studies in CKD patients [61].

In HUVECs, IS induced a decrease in endothelial proliferation and wound repair [62]. IS administration

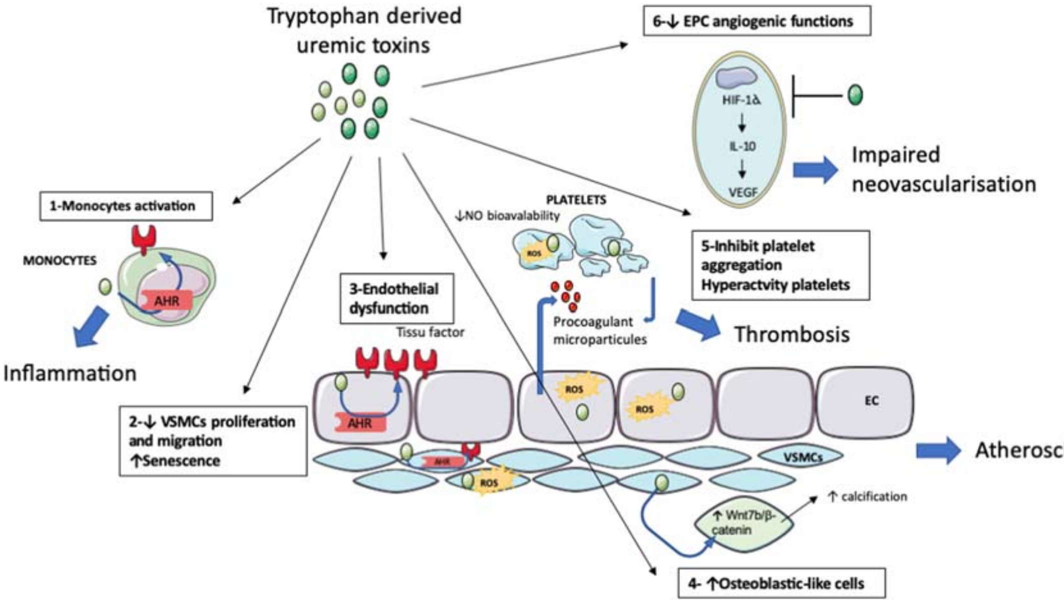
Tryptophan derived uremic toxins
6-↓ EPC angiogenic functions
HIF-1α
IL-10
VEGF
Impaired neovascularisation
1-Monocytes activation
MONOCYTES
AHR
Inflammation
PLATELETS
↓NO bioavalability
ROS
5-Inhibit platelet aggregation Hyperactvity platelets
3-Endothelial dysfunction
Tissu factor
Procoagulant microparticules
Thrombosis
2-↓ VSMCs proliferation and migration ↑Senescence
EC
VSMCs
Atherosclerosis
↑ calcification
↑ Wnt7b/β-catenin
4- ↑Osteoblastic-like cells

FIGURE 18.4 Schematic effect of tryptophan-derived uremic toxins in cardiovascular system. *AhR*, Aryl hydrocarbon receptor; *EC*, endothelial cell; *EPC*, endothelial progenitor cells; *HIF-1α*, hypoxia-inducible factor-1α; *IL-10*, interleukin 10; *NO*, nitric oxide; *ROS*, reactive oxygen species; *VSMCs*, vascular smooth muscle cells; *VEGF*, vascular endothelial growth factor.

increased the expression of adhesion molecules such as ICAM-1and E-selectin, which are involved in the pathophysiology and progression of atherosclerosis [63]. In HUVECs and human aortic smooth muscle cells, IS-induced IL-6 expression and ROS production are related to the activation of AhR through the activation of p65 (subunit of NF-κB) signaling transduction [64,65]. In HUVECs IAA triggered an inflammatory nongenomic AhR/p38MAPK/NF-κB pathway leading to the proinflammatory COX-2 upregulation that induced endothelial inflammation and oxidative stress [7]. Similarly, as observed in HUVECs, cardiomyocytes treated with IS showed an increased expression of cardiac hypertrophy- and fibrosis-related molecules through the activation of NF-κB and MAPKs pathways.

Acute exposure to IS induced the proliferation of VSMCs [66]. The proliferative effect of IS has been attributed the subsequent activation of different pathways, including MAPKs [36], AhR/NF-κB [67], and prorenin [68]. In contrast, chronic exposure to IS decreased VSMCs proliferation. These antiproliferative properties have been associated with elevated NADPH oxidase-dependent production of ROS [36] and upregulation of the cell cycle inhibitors p21 and p27 [69]. Long-term IS exposure also promoted VSMCs senescence [70]. Therefore the low level of VSMCs proliferation associated with long-term IS exposure might reflect a state of replicative senescence that follows the increase in proliferation associated with acute IS exposure.

In CKD mice, IS was shown to impair neovascularization in ischemic hindlimbs, while lowering serum IS levels using AST-120 could improve this condition [71]. Endothelial progenitor cells (EPCs) are pivotal in neovascularization. IS decreased the proangiogenic functions of EPCs by suppressing hypoxia-inducible factor-1α activation and consecutively the expression of IL-10 and vascular endothelial growth factor synthesis, known to be essential for EPCs mobilization and angiogenesis [71].

Vascular calcification

Vascular calcification is an independent risk factor for the development of cardiovascular (CV) diseases. In CKD patients, serum IS levels were independently correlated with aortic calcification suggesting that IS may act as a pro-calcifying toxin [3]. IS not only increases oxidative stress [72], but also the expression of bone-related proteins [73,74]. IS enhanced the transformation of aortic VSMCs into osteoblastic-like cells by activating Wnt7b/β-catenin expression [74]. IS increased inorganic phosphate-induced VSMCs calcification and osteogenic transdifferentiation. IS induced methylation and subsequent transcriptional suppression of the α-Klotho gene, which promoted vascular calcification in VSMCs cultures and in 5/6-nephrectomized rats [73]. IS suppressed the expression of fetuin-A via AhR signaling in human hepatoma HepG2 cells. Fetuin-A is a liver-derived circulating protein that has a potent calcification-inhibitory activity [75].

In a rat model, an IS exposure at serum levels similar to those experienced by hemodialysis patients significantly increased calcification in the aorta and peripheral arteries [40]. In this study, using a proteomic approach, an association between calcification events, coagulation, and glucometabolic signaling pathways was shown. Additional metabolic linkage to these pathways revealed that IS exposure engendered an insulin resistant state. Short-term exposure to IS before calcification had been established showed an activation of inflammation and coagulation signaling pathways in the aorta, demonstrating that these signaling pathways are causally implicated in IS-induced arterial calcification [40].

Tryptophan metabolites and cardiovascular events in CKD patients

High serum IS levels are associated with increased CV events [3] and patients with a history of CV diseases have higher serum IS concentrations than those without CV events [3]. Similarly, CKD patients with high serum IS levels presented a higher incidence of first heart failure event [6] and peripheral artery disease [76]. Serum IS level has been associated with the severity of coronary artery disease [77] and is an independent predictor for coronary restenosis in patients receiving drug-eluting stent-implantations [78]. A higher serum IS levels was significantly associated with an increased prevalence of diastolic dysfunction, despite preserved kidney function [79]. Another study revealed that, independent of kidney function, serum IS levels were significantly associated with CV events in patients with dilated cardiomyopathy [80]. Similarly, the accumulation of plasmatic IAA predicted CV diseases in CKD patients [7]. However, some studies suggested that IS/IAA were not associated with CV outcomes in hemodialysis patients [81,82]. These discrepant findings can be explained by a number of factors. During maintenance dialysis, IS could contribute to morbid events by causing a loss of RRF in response to its renal toxicity [52]. Therefore the presence or absence of RRF can be a major confounder in observational studies. In the HEMO study [82], IS was not associated with global mortality but with sudden cardiac death in patients with lower serum albumin (<3.6 g/dL). This observation was confirmed in another cohort of patients undergoing percutaneous revascularization for coronary artery disease or peripheral artery disease [83]. Because more than 90% of IS is bound to albumin, a lower albumin level may allow a higher free concentration of IS, potentiating its value as a prognostic factor for CV diseases [83].

Some preliminary observations suggest that IS accumulation may play a role in the development of arrhythmogenesis in CKD patients through atrial remodeling involving oxidative stress, inflammation, and profibrotic factors [84]. The depolarization of cardiomyocyte is significantly decreased after the administration of IS in animal models [85]. In good concordance, patients with corrected QT prolongation on the electrocardiogram had higher IS levels [85].

Similar associations have been found with the metabolites issued from the KYN pathway. 3-HKYN was higher in patients with CV disease [86] and was associated with an increase in early mortality in patients with a recent ischemic stroke independent from renal function [87]. In CKD patients, the TRP/KYN ratio was related to the carotid intima-media thickness, a presymptomatic predictor of atherosclerosis [88]. In CKD patients, a higher IDO activity was associated with a larger size of carotid plaques [89].

The hypothesis that AhR activation is involved in CV toxicity of TRP-derived uremic toxins has been confirmed recently. Sera from CKD patients displayed a strong AhR-activating potential (AhR-AP). AhR-AP was correlated with renal function and IS concentration. Survival analyses revealed that CV events were more frequent in CKD patients with an AhR-activating concentration above median [90].

Tryptophan metabolites involved in musculoskeletal disorders

The majority of studies highlighted the fact that TRP catabolites (mostly IS) play an important role in worsening bone mechanical properties by changing bone chemical composition and this may result in low bone turnover—a dynamic bone disease (Fig. 18.5). In mouse primary osteoblast culture, IS suppressed the expression of osterix, osteocalcin, and bone morphogenetic protein 2 mRNA and inhibited the formation of mineralized bone nodules. Although the molecular mechanisms that underlie the inhibition of differentiation are unclear. One hypothesis is the increase of oxidative stress induced by uptake of IS probably via AhR activation [91]. Osteoclasts and osteoblasts express OAT3 that allows IS uptake. IS reduced parathyroid hormone (PTH)-stimulated intracellular cyclic adenosine monophosphate production and decreased PTH receptor expression in osteoblastic cells. In osteoclasts, IS decreased JNK and ERK-phosphorylation as well as AP-1 DNA binding activity, which results in an alteration of their differentiation and function [92]. IS suppressed mRNA expression of receptor activator of NF-κB ligand, which is a pivotal factor for osteoclast differentiation via the AhR signaling pathway and reduced bone-resorbing activity of osteoclasts [92,93].

In a uremic animal model study, IS was shown to directly impact on bone elastic properties [94]. IS

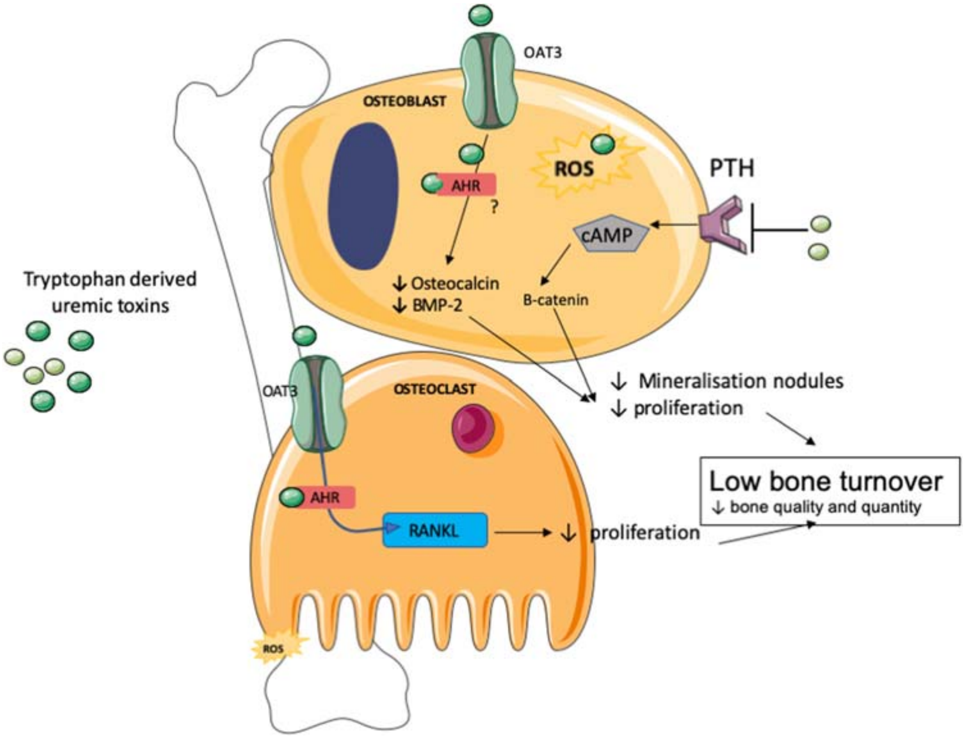

FIGURE 18.5 Impact of tryptophan-derived uremic toxins on bone metabolism. *AhR*, Aryl hydrocarbon receptor; *BMP2*, bone morphogenetic protein 2; *cAMP*, cyclic adenosine monophosphate; *OAT*, organic anion transporter; *PTH*, parathyroid hormone; *RANKL*, receptor activator of nuclear factor–κB ligand; *ROS*, reactive oxygen species.

decreased bone formation-related parameters in parathyroidectomized rats while bone resorption–related parameters were unchanged [95]. A cross-sectional study in hemodialysis patients found that serum IS was negatively correlated with bone formation markers, such as bone-specific alkaline phosphatase activity, and being independent of intact PTH levels [96]. Sclerostin, which has antianabolic effects on bone formation by inhibiting the Wnt/β-catenin pathway, was related to IS levels [97]. Some preliminary data suggest that IS can repress miR-29b microRNA precursor that negatively regulates the Wnt/β-catenin signaling [74].

Finally, in CKD rats, peripheral serotonin (5-HT) and its metabolite (5-HIAA) were increased. Both 5-HT and 5-HIAA were inversely associated with bone stiffness. These results must be confirmed in human [98].

Sarcopenia is frequently observed during CKD and the accumulation of TRP metabolites could participate to this phenotype by altering biologic functions and proliferation of muscle cells. In C2C12 myotubes, IS treatment induced a reticulum endoplasmic stress by increasing eukaryotic initiation factor 2 alpha phosphorylation and unfolded protein response. IS reduced myoblast determination protein 1 (myoD) expression, a key transcription factor involved in myogenic differentiation [99]. IS was reported to induce inflammatory cytokine expression (IL-6) and increase markers of muscle atrophy (myostatin and atrogin-1) [100]. IS-mediated myotube atrophy may happen through ROS-MAPKs [101,102]. IS induced mitochondrial dysfunction by decreasing the expression of the key mitochondrial protein peroxisome proliferator-activated receptor gamma coactivator 1-alpha. IS was able to trigger autophagy in addition to decreasing mitochondrial membrane potential [103]. IS decreased exercise capacity via the induction of muscle oxidative stress in CKD mice [102]. Furthermore, the administration of IS in mice was able to increase key atrogenes expression such as atrogin-1, which is involved in proteolysis and in a decreased muscle mass [100]. A significant inverse association between plasma IS levels and skeletal muscle mass was also observed in CKD patients [104].

Therapeutic strategies to reduce tryptophan metabolites accumulation and production

TRP metabolites have a high affinity with albumin (90%–95% in the case of IS/IAA) that explains their limited removal by classical dialysis since the free fraction is only able to diffuse across the dialysis membrane. Moreover, the free fraction decreases during dialysis, further reducing the clearance efficacy [10]. Even with "high efficiency" membranes, the dialytic clearance of protein bound-toxins is a very small fraction of the urea clearance [105]. Therefore innovative strategies to decrease the production of URS in hemodialyzed patients and patients not yet treated by dialysis are needed. Because the majority of TRP metabolites are produced by intestinal microbiota, strategies that could modulate microbiota composition appear to be an attractive idea. Nevertheless, the relations between features of the gut microbiota, uremic toxin production, and CKD progression have not been explored prospectively in human.

AST-120

AST-120 is an oral carbon adsorbent consisting of porous carbon particles, of approximately 0.2−0.4 mm in diameter, nonsoluble in water. Using a mass spectrometry approach, it was observed that AST-120 can adsorb at least 6 negatively charged and 17 positively charged URS, including TRP metabolites [106,107] with few adverse effects besides some constipation, nausea, or vomiting.

Several animal studies have demonstrated a beneficial effect of AST-120 in reducing toxic effect of TRP metabolites. AST-120 reduced vascular calcification [108], urinary albumin excretion, prevented glomerular sclerosis [109], decreased bone resistance to PTH [110], and improved muscle function [102,103]. Besides the adsorption of indole, AST-120 may induce a beneficial gut environment and decrease gut microbial fermentation of dietary TRP to indole [111].

Preliminary clinical trials in Japan suggested that AST-120 was effective in slowing the progression of renal disease and improving uremic symptoms [112]. However, this was not confirmed in the multinational, randomized, double-blind, placebo-controlled evaluating prevention of progression in CKD (EPPIC)-1 and EPPIC-2 trial that included 2035 adults, since no significant differences were observed [113]. The negative results of this study can be partially explained by the following: (1) the evolution of CKD in study subjects was less severe that was predicted; (2) the condition for initial dialysis was not identical within countries; (3) the deterioration of CKD in subjects and indicators of the severity of CKD were not consistent; and (4) the subjects showed poor compliance. Subsequent analyses revealed a significant reduction in the incidence of dialysis initiation in patients from AST-120 groups who succeeded to reach a compliance of 80% or greater. AST-120 seemed to be efficient to prevent kidney deterioration in a subgroup of patients with elevated proteinuria in addition to RAAS blockers [114]. Further studies on AST-120 are needed before generalization of its use.

Probiotics, prebiotics, and fecal microbiota transplantation

Probiotics are modified microorganisms expressing specific exogenous enzymes that are able to survive stomach acid and bile, to increase the colon concentration of symbionts, and confer a health benefit. Prebiotics are indigestible food additives that promote the selective growth of beneficial bacteria while limiting the proliferation of pathogenic bacteria.

Preliminary experimental strategies were very encouraging [17,115]. Most of these studies have demonstrated a decrease in TRP metabolites. First, small human studies were beneficial [116]. But later larger human trials have not been equally convincing. Table 18.1 summarizes randomized clinical studies reporting the use of prebiotics, probiotics, and symbiotics in CKD on trypotophan metabolites. In recent metaanalyses in CKD patients, no beneficial effects have been observed in favor of a reduction in IS production [117]. But the protocols were all relatively short in duration (less than 3 months), diverse compounds and doses of pre/probiotics, design and patient populations (CKD or dialysis patients). In hemodialysis patients, the baseline levels of toxins were higher, allowing for a more efficient effect to be observed. The galenic formula of probiotics seems important. Indeed, as compared with hemodialyzed patients receiving regular capsules, only those patients treated with gastroresistant seamless probiotic-containing capsules experienced a decrease in serum IS levels [116]. The failure of human studies testing probiotics alone could be explained by an unfavorable environment due to the whole-body urea, and hence, the colic fluid urea that may alter the symbiotic microbiota. Attempts to restore the desired microbiome by introducing favorable microorganisms without simultaneously improving the gut's biochemical milieu, for instance by using prebiotics, seem to be doomed to failure.

Fecal microbiota transplantation (FMT) may be an interesting option to modify gut microbiota. FMT has been associated with improved clinical outcomes, albeit only used in routine care for *Clostridium difficile* infection. However, so far there are no data on the use of FMT in CKD and specifically on URS production.

Low-protein diet and low-tryptophan diet

Because URS production is the consequence of amino acid transformation, decreasing protein intake may be a strategy to reduce TRP metabolites. Indeed, the poorly understood beneficial effects of low-protein diet (LPD) may be partially explained through such a mechanism.

TABLE 18.1 Randomized controlled human studies reporting the use of prebiotics, probiotics, and symbiotics in chronic kidney disease on trypotophan metabolites.

Reference	Treatment	Design	Results
Lopes et al. [118]	Symbiotic: 40 g of extruded sorghum plus 100 mL of unfermented probiotic milk	Single-center, double-blind, placebo-controlled $n = 58$, HD; 7 weeks	↓IS
Esgalhado et al. [119]	Resistant starch, 16 g/d	Single-center, double-blind, placebo-controlled $n = 31$, HD; 4 weeks	↓IS
Borges et al. [120]	Probiotic: *Streptococcus thermophilus*, *Lactobacillus acidophilus*, *Bifidobacterium longum*, 90 billion colony-forming units per day	Single-center, double-blind, placebo-controlled $n = 46$, HD; 3 months	No effect on IS
Ramos et al. [121]	FOS, 12 g/d	Single-center, double-blind, placebo-controlled, randomized, crossover $n = 50$, eGFR between <45 mL/min/1.73 m^2; 3 months	No effect on IS, IAA
Elamin et al. [122]	Gum arabic, 10–40 g/d	Single-center, open-label phase, randomized, $n = 36$, Stage 3B-4; 4 weeks	No effect on IS
Rossi et al. [123]	Symbiotic: *Lactobacillus*, *Bifidobacteria*, and *Streptococcus* genera + prebiotic (inulin, fructo-oligosaccharides, and galacto-oligosaccharides)	Single-center, double-blind, placebo-controlled, randomized crossover trial $n = 37$; CKD stages 4–5; 6 weeks	↓IS
Poesen et al. [124]	AXOS, 10 g twice daily	Single-center, double-blind, placebo-controlled, randomized, crossover $n = 40$, eGFR between 15 and 45 mL/min/1.73 m^2; 4 weeks	No effect on IS
Sirich et al. [125]	High-amylose corn starch (Hi-maize 260) 15 g/d	Single-center, double-blind, placebo-controlled $n = 40$, HD; 6 weeks	↓IS
Meijers et al. [126]	Oligofructose-enriched inulin (ORAFTI Synergy 1, Tienen, Belgium) 10 g twice daily	Single center, nonrandomized, open-label phase $n = 22$, HD patients; 4 weeks	No effect on IS

AXOS, Arabinoxylan oligosaccharides; *CKD*, chronic kidney disease; *eGFR*, estimated glomerular filtration rate; *FOS*, fructooligosaccharides; *HD*, hemodialysis; *IAA*, indole-3-acetic acid; *IS*, indoxyl sulfate.

High dietary proteins increase indole and IS production in healthy human [127]. LPD was efficient in reducing serum IS levels in CKD rats [128] and in hemodialysis patients [129]. However, it remains unclear if diet modulation could also affect the microbiota or if it is only the consequence of the reduction in protein intake. There are some preliminary data that observed a decrease in IS in mice fed with low-TRP diet [130]. However, in a small cohort of hemodialysis patients, no association between quantity of TRP intake and IS levels was observed [131]. Further studies are needed to confirm or infirm these preliminary results.

Other directions

Manipulation of the gut microbial TRP catabolism using specific mutant bacteria may be interesting. Devlin et al. have identified an abundant family of microbial tryptophanases within the human gut and demonstrated that altering the abundance of bacteria harboring tryptophanase activity can serve as a means of modulating IS production in gnotobiotic and conventional mice [132]. However, this strategy has not been explored in uremic conditions.

Besides microbiota modulation, decreased hepatic sulfation of indole and increased tubular secretion can represent new therapeutic targets. As indoxyl is sulfated in the liver, an inhibition of this pathway may be a novel therapeutic option. Rats with renal ischemia/reperfusion insult have been treated with phytochemical polyphenol compounds such as resveratrol or quercetin that show a potent inhibitory effect on SULT1A1. This strategy significantly inhibited hepatic production of IS [133]. Another treatment option is to facilitate the tubular excretion of IS directly through pharmacological intervention, by upregulating channels associated with IS secretion [134]. Developing specific inhibitor of key enzymes involved in the production of indole like TMO or tryptophanase should be developed in the future. Finally, the modulation of AhR activity could be proposed as a potential future target to decrease outcomes in CKD patients.

Conclusion

Although experimental data do convince us about the toxicity of TRP metabolites, these results must be demonstrated in human cohorts. Indeed, TRP metabolites can be considered only as a marker of kidney failure, and there is a plethora of other retained compounds that could play a role in uremic related complications, either directly or indirectly.

The interaction between diet and gut microbiota must be investigated in CKD. The reduction in protein intake is probably one of the major therapeutic interventions to reduce TRP metabolites production in CKD. Although several bacteria capable of producing TRP catabolites have been identified, in the human gut, the main contributors remain to a large extent unknown. The fecal metagenomic data are still lacking during human CKD. In the future, a combined analysis of profiled microbes (metagenomics) along with the TRP catabolites production (metabolomics) from CKD patients' stool samples seems to be of major importance and may enable the development of specific tools to modulate intestinal microbiota. With all these new strategies, we hope to decrease the progression of not only CKD but also CV diseases, bone diseases, and sarcopenia.

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CHAPTER

19

Alkalization to retard progression of chronic kidney disease

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Introduction

Chronic kidney disease (CKD) progression from early to advanced stages is increasing [1,2] as is albuminuria [2] and its associated death rate [3]. Progression to advanced CKD augments cardiovascular disease (CVD) mortality risk prediction by traditional CVD risk factors, including diet [2,4,5]. Indeed, individuals with CKD suffer premature death more commonly than developing end-stage kidney disease (ESKD) [6]. This enhanced mortality is due predominantly to increased risk for, and earlier onset of, CVD [2], including myocardial infarction [7] and stroke [8]. US populations that are at particularly high ESKD risk are so because of faster progression of prevalent CKD to ESKD rather than to greater CKD prevalence [9], thereby contributing to increasing ESKD prevalence [1]. These observations support an increasing focus on addressing factors that contribute to progression of prevalent CKD to ESKD.

There is growing evidence that an acid (H^+) milieu augments CKD progression and that reducing it is kidney protective. Beginning with the most severe end of the spectrum of what we will call "H^+ stress" (Fig. 19.1), treatment of CKD-related metabolic acidosis in patients with plasma total CO_2 ($PTCO_2$) <22 mM as recommended by KDIGO guidelines [10] appears to slow decline rate of creatinine clearance [11] and estimated glomerular filtration rate (eGFR) [12,13] in individuals with very low GFR. Correction of less severe metabolic acidosis (i.e., $PTCO_2$ 22−24 mM) than that for which current guidelines recommend treatment also appears to slow eGFR decline [14]. In addition, alkali treatment of individuals with reduced eGFR and normal $PTCO_2$ but eating the high H^+ diets of developed societies [15] appears to slow eGFR decline [16]. These studies support that the full spectrum of H^+ stress ranging from high dietary H^+ with initially normal $PTCO_2$ to individuals with modestly reduced eGFR and normal $PTCO_2$ to those with very low eGFR and low $PTCO_2$ is harmful to kidneys and that its amelioration with dietary alkali slows CKD progression.

Overview of acid−base balance

Optimal cell and tissue function requires maintenance of "free" body fluid hydrogen ion concentration ($[H^+]$) within a relatively narrow, slightly alkaline, range compared to pure or "neutral" H_2O with $[H^+] = 100\ \text{nM}$ or $100 \times 10^{-9}\ \text{M} = 10^{-7}\ \text{M} = 10^{-7}\ \text{mol/L}$. Because pH of an aqueous solution is its negative log in mol/L, pure or "neutral" H_2O has $\text{pH} = 7.00$. "Free" H^+ appears to be the component of body H^+ that mediates its physiologic and pathophysiologic actions and so its measurement is of significant interest to clinicians. Nevertheless, most body H^+ is bound to other moieties (i.e., is "buffered") and so is not "free" in solution. Although buffered H^+ appears to have less direct physiologic and/or pathophysiologic actions, its buffering can cause tissue damage as in consumption of the

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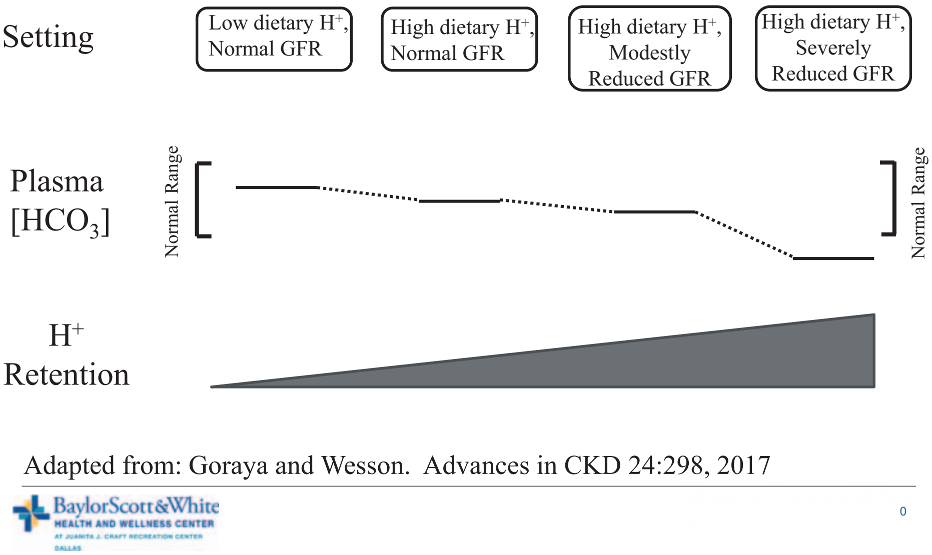
Setting
Low dietary H+, Normal GFR
High dietary H+, Normal GFR
High dietary H+, Modestly Reduced GFR
High dietary H+, Severely Reduced GFR
Plasma [HCO3]
Normal Range
Normal Range
H+ Retention
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Adapted from: Goraya and Wesson. Advances in CKD 24:298, 2017

FIGURE 19.1 Theoretical construct for CKD-related acid (H^+) stress continuum. *CKD*, Chronic kidney disease.

mineral content of bone [17,18] and the degree of H^+-buffering might initiate signaling of downstream actions such as increased kidney acidification [19].

Under normal steady-state conditions, multiple systems maintain human plasma [H^+] within 35–45 nM (pH 7.46–7.35), with "normal" considered [H^+] = 40 nM or pH = 7.40. Clinicians have access to plasma as their "window" into an individual's acid–base status but other compartments, like the interstitial compartment of extracellular fluid, are also affected by challenges to systemic acid–base and likely play important contributory roles to body responses to these challenges. Acidosis is a process characterized by a net gain of H^+ (caused by gain of H^+ or by loss of buffer, most commonly HCO_3). On the other hand, the process characterized by a net loss of H^+ (caused by gain of base, typically HCO_3, or loss of H^+) is known as alkalosis. Despite daily acid–base challenges from diet and cellular metabolism, various body response strategies typically maintain plasma [H^+] within the normal range.

Some chronic conditions, including CKD with severely decreased GFR, are associated with such high H^+ accumulation that it is characterized by an initial decrease in plasma bicarbonate (nearly identical, but only slightly less in amount, to $PTCO_2$) concentration ([HCO_3]), the type of acidosis known as *metabolic* acidosis. Because diets typical of developed societies are H^+-producing [15], residents in such societies are chronically challenged with dietary H^+. This "fixed" (or "nonvolatile" to distinguish it from acidosis due to accumulation of carbon dioxide gas that is called *respiratory* acidosis) H^+ is excreted predominantly by the kidney. Some mechanisms employed by kidneys to excrete the ingested H^+ yield the short-term benefit of enhanced H^+ excretion but the long-term detriment of chronic kidney injury [19]. On the other hand, some individuals with less severely decreased GFR and eating H^+-producing diets accumulate H^+ at levels that can cause kidney injury [16] yet are insufficient to reduce $PTCO_2$, a condition characterized as H^+ retention [20].

Epidemiology of the spectrum of "H^+ stress"

Most individuals with CKD have sufficient remaining eGFR that enables them to excrete H^+ generated by the H^+-producing diets of developed societies and endogenous metabolic processes to avoid progressive H^+ retention and consequently do not have steady-state metabolic acidosis [17,21]. Metabolic acidosis of CKD is typically defined as a $PTCO_2 < 22$ mmol/L due to reduced eGFR (and not to other concomitant conditions like severe diarrhea) and not to respiratory alkalosis [22]. Metabolic acidosis appears after an as yet incompletely determined threshold of accumulated H^+ exhausts multiple compensatory mechanisms [23]. Using the $PTCO_2 < 22$ mmol/L threshold, most CKD patients do not have metabolic acidosis but its incidence increases as eGFR declines [24]. Overall, about 15% of patients with CKD have metabolic acidosis [24,25] but about 37% of individuals with stage 4 CKD (eGFR 15–29 mL/min/1.73 m^2) have metabolic acidosis [25]. Individuals with stage 4 CKD have sevenfold higher and those with stage 3 CKD (eGFR 30–59 mL/min/1.73 m^2) have twofold, respectively, higher odds of metabolic acidosis than those with stage 2 (eGFR 60–89 mL/min/1.73 m^2) CKD [25]. Individuals with CKD, severely reduced eGFR, and metabolic acidosis have increased urine indices of kidney injury that are reduced with oral alkali-induced improvement of their metabolic acidosis [12].

Reduced residual H^+ excretory capacity, largely determined by level of remaining eGFR, and high dietary H^+ intake contribute to the risk for developing metabolic acidosis. Regarding the former, reduced ammonium excretion appears to identify individuals at risk for developing metabolic acidosis [26]. For example, the risk of incident metabolic acidosis was 2.5-fold higher if ammonium excretion was <15 mEq/day in African American Study of Kidney Disease and Hypertension participants after controlling for GFR and other potential confounders [26]. Regarding the latter, higher dietary H^+ was inversely associated with $PTCO_2$, even among individuals without CKD [27–30], and was more likely to cause metabolic acidosis in patients with CKD who had lower compared to those with higher eGFR [31].

Diets typical of developed societies are H^+-producing because of the preponderance of H^+-producing meats and refined grains compared to base-producing fruits and vegetables [15]. Individuals eating such diets can have H^+ retention [32–36], with magnitude inversely related to eGFR [34], that is not reflected by plasma acid–base parameters characteristic of metabolic acidosis. Low urine citrate excretion might identify H^+ retention in these patients with CKD but no metabolic acidosis [35,36] and thereby identify them as potential candidates for alkali therapy for kidney protection. Patients with CKD given an increment in dietary H^+ cumulatively excrete less H^+ than ingested, consistent with H^+ retention [17,37]. Individuals with CKD and modestly reduced eGFR without metabolic acidosis despite eating a high H^+ diet nevertheless have increased urine indices of kidney injury that are reduced with oral alkali [16,38].

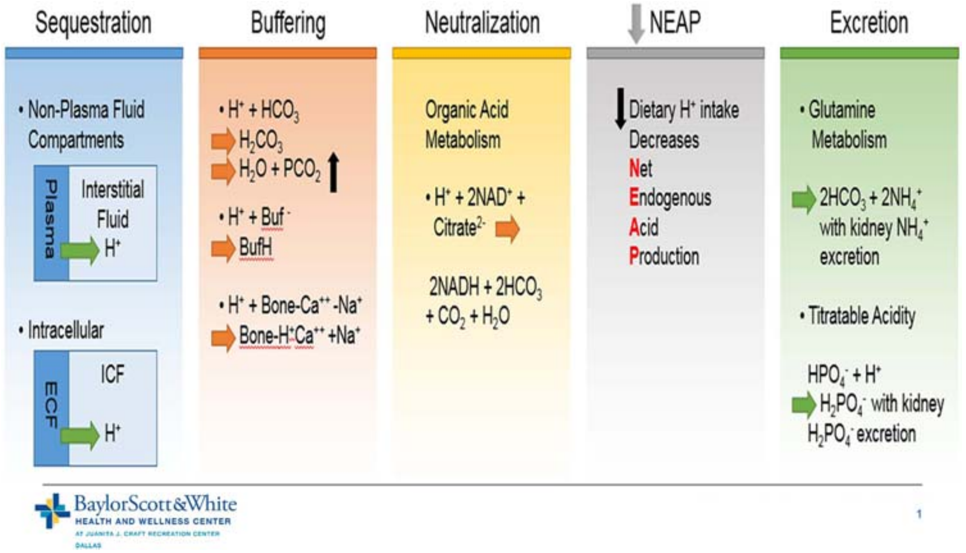
High H^+ diets given to animals with normal GFR that increase urine H^+ excretion without causing metabolic acidosis by plasma acid–base parameters nevertheless decrease plasma base excess and increase H^+ content of kidney interstitial fluid [39]. Such diets also increase urine indices of kidney injury in animals with normal GFR [23]. Furthermore, high H^+ diets are associated with increased CKD incidence [40]. These data suggest that high H^+ diets cause pathologic H^+ accumulation even in individuals with normal GFR and constitute an early phase of the spectrum of H^+ stress.

The full spectrum of H^+ stress (Fig. 19.1), including (1) high H^+ diets in individuals with normal eGFR, (2) those eating high H^+ diets with reduced eGFR without metabolic acidosis but with H^+ retention, and (3) those individuals with more severely reduced eGFR with metabolic acidosis, all appears to risk H^+-related kidney injury. The high H^+ diets of developed societies appear to subject these populations to some, at-present unknown, level of CKD risk. Epidemiologic studies support that high H^+ diets increase the progression risk to ESKD in the general population [41,42]. Those with H^+ retention appear to be individuals for whom oral alkali might provide kidney protection [16] but whose population frequency is unknown at present. The ~15% of CKD patients with metabolic acidosis are more clearly at CKD risk, current treatment guidelines recommend treatment when $PTCO_2$ is <22 mM, and alkali treatment appears to be kidney protective [11–13].

The daily H^+ challenge

Fig. 19.2 depicts mechanisms by which the body mitigates fixed H^+ challenges to acid–base balance and thereby helps avoid metabolic acidosis, using strategies, including (1) buffering accumulated H^+; (2) sequestering H^+ away from plasma to other fluid compartments, including interstitial and intracellular fluid; (3) neutralization of accumulated H^+ through liver metabolism of endogenous and exogenous base-producing substances like citrate in many plant-based foods, including most fruits and vegetables, and of some organic products of intrinsic metabolism like lactic acid to yield HCO_3; (4) reduction of net endogenous acid production (NEAP); and (5) urine H^+ excretion (about 1 mEq/kg/day) [43] derived from liver metabolism of H^+-producing food components (like animal-sourced protein) and some endogenous metabolic products, both of which increase NEAP. Net excretion of fixed H^+ from the body by the kidney yields regeneration of new HCO_3 that restores HCO_3 lost through titration by added H^+. Dietary sodium chloride (NaCl) also increases NEAP [44].

Diets typical of developed societies are H^+-producing because of the preponderance of H^+-producing animal-sourced food components compared to base-producing plant-sourced components [45]. Animal-sourced compared to plant-sourced food components have more protein and the protein has more sulfur-containing amino acids (e.g., methionine and cysteine) that when metabolized yield sulfuric acid. On the other hand, most fruits and vegetables have fewer sulfur-containing amino acids and potassium salts of organic acids (e.g., citrate) that when metabolized yield HCO_3. Even fresh animal-sourced foods contain various amounts of NaCl, whereas fresh fruits and vegetables are very low in Na^+ and Cl^-. Processed foods from animal and plant sources constitute an increasing proportion of developed society diets and have added NaCl. Dietary fats and sugars contribute comparatively less to net H^+ production when completely metabolized. The preponderance of animal-sourced to plant-sourced foods, of processed to fresh foods, and high NaCl content all contribute to the H^+-producing nature of diets typical of developed



Sequestration

- Non-Plasma Fluid Compartments

Plasma | Interstitial Fluid → H^+

- Intracellular

ECF | ICF → H^+

Buffering

- $H^+ + HCO_3$ → H_2CO_3 → $H_2O + PCO_2$ ↑
- $H^+ + Buf^-$ → BufH
- H^+ + Bone-Ca^{++}-Na^+ → Bone-H:Ca^{++} +Na^+

Neutralization

Organic Acid Metabolism

- $H^+ + 2NAD^+$ + Citrate^{2-} →

$2NADH + 2HCO_3 + CO_2 + H_2O$

↓ NEAP

↓ Dietary H^+ intake Decreases **N**et **E**ndogenous **A**cid **P**roduction

Excretion

- Glutamine Metabolism

→ $2HCO_3 + 2NH_4^+$ with kidney NH_4^+ excretion

- Titratable Acidity

$HPO_4^- + H^+$ → $H_2PO_4^-$ with kidney $H_2PO_4^-$ excretion

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FIGURE 19.2 Body strategies to mitigate added H^+: maintenance of normal acid–base homeostasis.

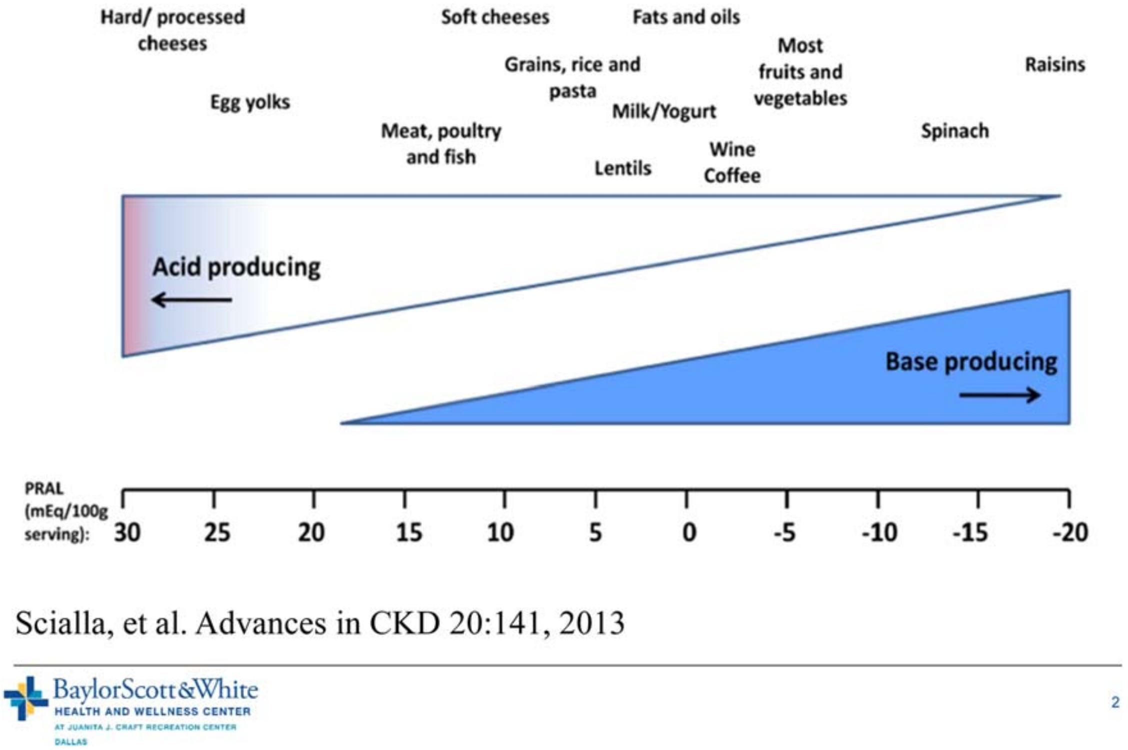

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FIGURE 19.3 Contribution of foods to dietary acid load. *DAL*, Dietary acid load.

societies. Fig. 19.3 shows comparable acid- and base-producing capacity of selected foods.

Retarding CKD progression through a more alkali-producing diet includes limiting food components that yield H^+ when metabolized like animal protein, including dairy products, most grains, and lentils [45] as well as limiting dietary NaCl that increases NEAP [44]. On the other hand, increasing intake of base-producing foods also increases dietary alkali but their base-producing capacity varies (see Fig. 19.3). Foods with high base-producing capacity comprise many fruits and vegetables, including raisins, cruciferous vegetables (e.g., broccoli, brussels sprouts, cabbage), leafy greens (kale, spinach, lettuce, collard greens), and soy protein [46]. Substituting base-producing for acid-producing food is a particularly effective strategy for dietary H^+ reduction [15].

Maintenance of normal acid−base homeostasis

Steady-state maintenance of systemic acid−base status occurs through integration of physiologic mechanisms such as extra- and intracellular buffering processes and collaborative actions of the kidney, liver, lung, gastrointestinal tract, and skeleton. Accordingly, excess H^+ accumulation becomes evident to clinicians through changes in plasma acid−base parameters when the accumulated H^+ exceeds the capacity of normal homeostatic mechanisms and/or because these homeostatic mechanisms are compromised. To understand better how clinicians could manage H^+ accumulation that might exacerbate CKD progression, let us examine the body's various responses to ameliorate untoward effects of accumulated H^+ (Fig. 19.2).

H^+ buffering

HCO_3/H_2CO_3 buffer system. Adding H^+ to body fluids containing HCO_3 leads to the following:

$$H^+ + HCO_3 \rightarrow H_2CO_3 \rightarrow H_2O + CO_2\uparrow \text{ (lungs excrete } CO_2 \text{ gas from the body)}$$

Consequently, the body effectively removes added H^+ from plasma as CO_2 gas that would otherwise yield H^+ (in a reversal of the abovementioned equation) if it were to accumulate, avoiding the other type of acidosis, respiratory acidosis. This rapidly responsive system works well to minimize the increase in $[H^+]$ (=decrease in pH) that would otherwise occur in the absence of this elegant system. The price paid is a reduction in plasma $[HCO_3]$ that kidneys must regenerate through H^+ excretion (see next).

Non-HCO_3 buffers. "Free" H^+ determines the acid−base effect on cell and tissue function. Binding H^+ to buffers removes it from solution and diminishes its untoward effects. The major non-HCO_3 extracellular buffers are hemoglobin and albumin whereas phosphate ion and anionic proteins are the major non-HCO_3 intracellular buffers. Patients with CKD commonly have decreased plasma hemoglobin and albumin, compromising extracellular buffering capacity. Quantitatively, most H^+ binding to non-HCO_3 buffers occurs intracellularly [47]. Bone calcium carbonate and dibasic phosphate are important buffers for both acute and chronic metabolic acidosis [17]. Animals given an increment in dietary H^+ that increased steady-state urine net acid excretion (NAE) but did not change steady-state plasma acid−base parameters, including $PTCO_2$, nevertheless had decreased plasma blood base excess [39], consistent with increased titration of non-HCO_3 buffers. By contrast, animals given aldosterone and Na_2SO_4 to increase urine NAE without an increment in dietary H^+ did not have decreased blood base excess [39], supporting the importance of accumulated H^+, and not simply ongoing enhanced urine NAE per se, as the factor that led to titration of non-HCO_3 buffers.

H^+ sequestration into interstitial fluid

The interstitial component of the extracellular fluid compartment is separated from the vascular component at the tissue level of organs by capillary basement membranes. Kidney interstitium occupies strategic space between peritubular capillaries and kidney tubules, facilitating potential chemical and cytokine communication between plasma and tubule fluid [48]. Microdialysis of the kidney cortex allows assessing of the chemical and cytokine content of the kidney interstitium [49]. Animals given an increment in dietary H^+ that increased steady-state urine NAE but did not change steady-state plasma acid−base parameters, including $PTCO_2$, nevertheless had increased H^+ content of kidney cortical interstitial fluid assessed with microdialysis [39]. This H^+ retention in response to dietary H^+ was greater in animals with reduced GFR, even when plasma acid−base parameters were not different from control [23]. Skeletal muscle also had H^+ retention [50], supporting that H^+ retention is a systemic phenomenon, at least in the setting of reduced GFR. Importantly, H^+ retention persisted until the dietary H^+ increment discontinued or was counterbalanced by added dietary alkali [23]. Excess body H^+ sequestered from plasma in interstitial fluid might have the benefit of minimizing H^+ accumulation in plasma with its possible untoward consequences while simultaneously stimulating basolateral kidney tubule mechanisms that enhance H^+ excretion [51−53].

Even large increments in dietary H^+ lead to little to no measurable changes in plasma acid−base parameters in individuals in developed societies, and the small changes that occur typically do so within the normal ranges of clinical laboratories [54]. In addition, increasing H^+ retention that occurs over time with decreasing eGFR is associated with minimal changes in $PTCO_2$ within the normal range for clinical laboratories [34,36]. These data show the effectiveness of body systems to maintain $PTCO_2$ in response to an H^+ challenge but also highlight the clinician's challenge to gauge dietary H^+ by plasma acid−base parameters. On the other hand, CKD patients with reduced GFR can have greater increases in plasma $[H^+]$ and greater decreases in $PTCO_2$ in response to the same increment in dietary H^+, even developing metabolic acidosis, at levels of dietary H^+ that do not cause metabolic acidosis in patients with higher GFR [31]. Consequently, clinicians are more likely to recognize metabolic acidosis in patients with lower than higher GFR.

Endogenous H^+ neutralization

The earlier stage in the spectrum of H^+ accumulation that is insufficient to manifest as metabolic acidosis, which we call H^+ retention, nevertheless is sufficient to increase urine levels of substances associated with progressive eGFR decline like endothelin and aldosterone [32] and with increased urine biomarkers of kidney injury [38]. Untoward effects of accumulated H^+ might be ameliorated through neutralization by base derived by metabolism of endogenous and exogenous substances.

The pH-sensitive metabolite citrate is the most abundant organic base equivalent in the urine, is freely filtered at the glomerulus, and the extent of its proximal tubule reabsorption determines its urinary excretion [55]. Secreted H^+ from proximal tubule cells into luminal fluid partially titrates filtered citrate from its trivalent (citrate^{3-}) to divalent (Hcitrate^{2-}) form, the latter being the preferred substrate for the apical Na^+ dicarboxylate cotransporter, NaDC-1, which reabsorbs it [56,57]. Cytoplasmic ATP citrate lyase metabolizes reabsorbed citrate to oxaloacetate and acetyl-CoA or transports it into mitochondria, where it enters the tricarboxylic acid cycle [58]. When citrate is converted to glucose or CO_2 and H_2O, 2 or 3 H^+ are consumed depending on the valence of the citrate anion, generating 2 or 3 HCO_3^- per citrate molecule. Citrate reabsorption, therefore, equals base gain but its excretion represents base loss [59]. Individuals with reduced eGFR who are eating a high H^+ diet who have H^+ retention but no metabolic acidosis have reduced urine citrate excretion [35,36]. The retained citrate can be metabolized to yield HCO_3 to neutralize H^+ that accumulates as eGFR declines [36].

Reduced NEAP

Individuals with increased NEAP, as might be the case in those eating the high H^+-producing diets typical of developed societies, reduce NEAP in response to an additional H^+ challenge [60]. By contrast, in individuals with low baseline NEAP, as might be the case in those eating a base-producing diet, this response is blunted [60].

Enhanced urine H^+ excretion

Importance of urine buffers in kidney H^+ excretion

The kidney is the main contributor to excretion of metabolically produced fixed H^+. Diets of individuals in developed societies typically produce the equivalent of 60–100 mmol of H^+ daily when metabolized. To excrete 100 mmol of free H^+ in a typical daily urine volume of 1 L would require excreted urine to have a $[H^+] = 100\ \text{mmol/L} = 100 \times 10^{-3}\ \text{M} = 10^{-1}\ \text{M} = \text{pH}$ of 1.0 (remember that pH is the negative log of the $[H^+]$ in mol/L). Because humans are unable to reduce urine pH below 4.0 (=$[H^+]$ of 10^{-4} M) that is equal to $[H^+]$ of 0.1 mM = 0.1 mmol/L, to excrete 100 mmol of the daily H^+ generation in urine with pH 4.0 would require $100\ \text{mmol}/0.1\ \text{mmol/L} = 1000\ \text{L}$ of urine! Hence, kidneys excrete fixed H^+ predominantly as H^+ bound to buffers, not as free H^+ in solution. Quantitatively, ammonium [NH_4^+ from $NH_3 + H^+$] is the most important urine buffer, particularly in response to increments in dietary H^+, followed by "titratable acidity," most of the latter being phosphate ($HPO_4^{=} \rightarrow H_2PO_4^-$).

Afferent signal for H^+ secretion

The signal(s) that tell kidneys to increase overall urine H^+ excretion in response to (1) an increment in dietary H^+ with normal GFR but in the absence of metabolic acidosis; (2) a reduced functioning nephron capacity (reduced GFR) in the setting of the typical H^+-producing diet of developed societies (which requires greater per nephron H^+ excretion to achieve the same overall H^+ excretion as when there was a full contingent of functioning nephrons) but no metabolic acidosis; or (3) metabolic acidosis, whatever the underlying GFR, are not clear. Nevertheless, the interstitial fluid compartment appears to be an appropriate one from which an afferent signal might initiate a change in kidney tubule acidification in response to the three settings described. Unlike plasma, interstitial fluid is comparatively protein-free, making its $[H^+]$ very sensitive to H^+ addition or removal, unlike the highly buffered plasma compartment. Consequently, even small amounts of H^+ added to the interstitial compartment will cause comparatively large changes in $[H^+]$. This arrangement makes the interstitial fluid compartment a better one in which to house the "acidstat" than plasma to monitor acid–base status and respond with a signal to change tubule acidification. Were plasma to be the main or exclusive compartment housing the "acidstat," wide swings in free $[H^+]$ would have potentially catastrophic consequences to physiologic function. Microdialysis reveals dramatic increases in interstitial $[H^+]$ induced by increments in dietary H^+ that cause no to comparably small changes in plasma acid–base parameters [39]. We hypothesize that pH sensors such as GPR4 [61] sense these $[H^+]$ changes in the interstitial fluid compartment. Other or additional signals might be the degree of titration of body buffers [39].

Efferent response leading to increased kidney tubule acidification

As discussed, metabolically produced H^+ titrates body fluid HCO_3, thereby reducing their concentration. This means that were kidneys to only recover HCO_3 that was filtered into its tubules, there would be a progressive body HCO_3 deficit because of ongoing metabolic H^+ production with progressive titration and reduction of body fluid HCO_3. This reminds us that kidneys must not only *recover* filtered HCO_3 but must also *regenerate* new HCO_3 to replace that lost through H^+-titration as described. These two main kidney tasks are accomplished by H^+ secretion from kidney tubule cells into the tubule lumen. When there is a high amount of HCO_3 in the tubule lumen as is the case in the proximal tubule, secreted H^+ titrates luminal HCO_3 to CO_2 and H_2O as described and CO_2 gas diffuses into the cell and is reconstituted to HCO_3 by the enzyme carbonic anhydrase. Reconstituted HCO_3 transports across basolateral membranes of tubule cells to return to the systemic circulation. When tubule HCO_3 content is low as in the distal nephron, most secreted H^+ titrates non-HCO_3 buffers that are excreted in the urine, mostly as $NH_4{}^+$ and titratable acidity. Exit of secreted H^+ from the body as described allows for HCO_3 to be regenerated. Overall, the process is called NAE and is equal in amount to HCO_3 regeneration. Increments in NAE promoted by increments in dietary H^+ intake are mediated mostly by increased glutamine metabolism with increased urine $NH_4{}^+$ excretion and with smaller contributions from increased titratable acidity and decreased urine excretion of HCO_3 [21]. Most patients with CKD and reduced GFR can achieve steady-state H^+ excretion enough to avoid progressive metabolic acidosis while eating H^+-producing diets [17,21]. More advanced GFR reduction in CKD patients, however, is associated with reduced urine $NH_4{}^+$ excretion [26,33] that likely contributes to their progression along the H^+ stress spectrum from worsening H^+ retention eventually to metabolic acidosis.

Kidney response to H^+ accumulation

Accumulating H^+ activates kidney paracrine hormones, including angiotensin II (AII), aldosterone, and endothelin-1 (ET-1), which all mediate enhanced kidney H^+ excretion [51–53,62,63]. The increment in urine H^+ excretion is mediated predominantly by increased urine ammonium excretion [21]. These responses provide the short-term benefit of increased H^+ excretion but appear to be accompanied by the long-term detriment of progressive CKD progression mediated by interstitial fibrosis and inflammation [64–66].

Angiotensin II

Dietary H^+ increases kidney AII levels [63] that stimulate distal [63] and proximal [67] tubule H^+ secretion through upregulation of the Na^+/H^+ exchangers NHE3 and NHE2. In contrast, alkali supplementation in CKD patients with metabolic acidosis [14] and in animal CKD models [63] with oral Na^+-based alkali or base-producing food components reduces elevated kidney AII levels measured by microdialysis or with urine angiotensinogen, the latter being a surrogate of kidney AII levels. Because a persistent increase in kidney AII levels can cause interstitial inflammation, fibrosis, tubular atrophy, and proteinuria that progressively reduce kidney function [68–70], lowering AII levels with dietary H^+ reduction done either with Na^+-based alkali or base-producing food components appears to be kidney protective. Because AII increases kidney production of ET-1 [71], aldosterone [72], and stimulates ammoniagenesis [67], it might play a central role in CKD progression and its reduction with dietary alkali might be key component of kidney protection in CKD.

ET-1 and aldosterone

Kidney levels of both ET-1 and aldosterone are elevated in experimental CKD models [62,66] and urine levels are elevated in patients with CKD [32]. These substances help mediate increased nephron acidification of animals with reduced nephron mass [62] but contribute to progressive GFR decline in these same models [66]. Dietary H^+ reduction with oral alkali [50,65] or base-producing diets [50] reduce kidney levels of these substances in these experimental CKD models. In addition, oral Na^+-based alkali reduces urine excretion of both in patients with CKD [32]. These data support that the kidney protective benefit of dietary H^+ reduction is mediated in part through reduced kidney levels of ET-1 and aldosterone.

Ammoniagenesis

Although total ammonium excretion decreases as CKD worsens [26,33] due to reduced ammoniagenesis [73], ammonia generation per functioning nephron increases, helping to maintain H^+ excretion in the setting of reduced eGFR [21,73]. This adaptive response helps with the short-term need to increase per nephron H^+ excretion in the setting of reduced nephron mass and continued high dietary H^+ intake. Nevertheless, over the long term, this adaptive response contributes to progressive nephron loss because ammonia activates the alternative complement pathway within the kidney, increasing inflammation and increasing tubulointerstitial damage [64]. Oral Na^+-based alkali reduces ammoniagenesis in experimental CKD models and thereby reduces interstitial injury with amelioration of subsequent GFR decline [64].

Alkali management strategies to retard CKD progression

The most recent practice guidelines from the National Kidney Foundation [74] recognize two strategies by which to reduce H^+ stress: reduce NEAP and/or neutralize accumulated acid with Na^+-based alkali. Regarding reducing NEAP with diet, the guidelines *suggest* doing so in adults with CKD stages 1–4 "through increased dietary intake of fruits and vegetables (2C) in order to reduce the rate of decline of residual kidney function." The "2C" grading acknowledges the need for more published research in this area such that the true effect may be substantially different from the estimate of the effect. Regarding reducing NEAP with Na^+-based alkali, the guidelines *recommend* doing so in adults with CKD stages 3–5 "through increased bicarbonate supplementation (1C) in order to reduce the rate of decline of residual kidney function." The "1C" grading again acknowledges the need for more published research in this area so that the true effect may be substantially different from the estimate of the effect. Regarding a target level of serum HCO_3 to seek to achieve with Na^+-based alkali, the guidelines offer the *opinion* that "it is reasonable to maintain serum bicarbonate levels at 24–26 mmol/L." The "opinion" grading recognizes that the available evidence is insufficient to offer a more definitive target. Recommended $NaHCO_3$ doses from earlier recommendations [10] range from 0.5 to 1.0 mmol HCO_3 or its equivalent per kg lean body weight daily.

Recognizing that H^+ accumulation contributes to CKD progression, we categorize approaches to reduce H^+ accumulation as a strategy by which to retard CKD progression into three general categories:

- Reduce H^+ intake.
- Neutralize accumulated H^+.
- Remove accumulated H^+.

Reduce H^+ intake: dietary management of H^+ accumulation

As noted, typical diets in developed societies are H^+-producing, due largely to the proportionately greater amount of animal-sourced proteins (which are H^+-producing) than plant-sourced proteins (many of which are base-producing). Plant-sourced dietary protein interventions not only reduced H^+ production from sulfur- and phosphate-containing amino acid metabolism, improved metabolic acidosis [75], and reduced H^+ retention [35] in individuals with CKD, but also improved weight, blood pressure, and other cardiovascular risk parameters [75,76]. The strategy discussed next supports diet as the foundational "food first" [77] approach to management of patients with CKD, including avoiding or managing H^+ accumulation, with pharmacologic therapy as adjunctive to diet.

These dietary strategies mainly include:

1. reducing H^+-producing food components like animal-sourced protein,
2. limiting dietary NaCl, and
3. adding base-producing food components like fruits and vegetables.

High dietary H^+ contributes to metabolic acidosis in individuals with severely reduced GFR [15,31] and to H^+ retention in those with more modest eGFR reduction [32,34–36]. The above mentioned three strategies and/or combinations thereof can accomplish dietary H^+ reduction.

Removing/limiting H^+-producing dietary components

Acid contents of many foods have been published [45] and can be used to limit intake of high H^+-producing foods for individuals with CKD. These H^+-producing food components include mainly animal-sourced protein. When animal-sourced protein is prescribed, fresh rather than processed food is recommended because of lower NaCl and Na^+ phosphate that are often added to such food to preserve shelf life can increase NEAP [44]. Individuals with CKD given a vegetarian diet supplemented with keto-analogs had better eGFR preservation than equivalent participants given a low-protein diet with a mixture of animal- and plant-sourced proteins [78].

Limiting dietary NaCl

As noted, dietary NaCl increases NEAP [44] and so its reduction contributes to dietary H^+ reduction. When fresh fruits and vegetables were added to diets of individuals with CKD and metabolic acidosis, study participants substituted these food components given at no cost for more expensive, processed food components that they had previously purchased, leading to decreased NaCl intake [14,38]. Therefore increasing the proportion of fresh plant-sourced foods in the diet, which are naturally low in NaCl, might help reduce NaCl intake, additionally reducing the dietary H^+ load.

Adding base-producing food components like fruits and vegetables

Dietary base-producing fruits and vegetables given to nondiabetic patients with stage 4 CKD and serum $HCO_3 < 22$ mEq/L in amounts designed to reduce their dietary H^+ intake by 50% improved metabolic acidosis comparable to similar individuals given $NaHCO_3$ [75]. Estimated GFR was not different between both interventions and both treatments were associated with lower-than-baseline urine indices of kidney injury, including albumin, *N*-acetyl-beta-*d*-glucosaminidase (NAG), and TGF-β [75]. In other studies, individuals with CKD stage 3 and low normal serum HCO_3 (22–24 mEq/L), a level higher than that for which earlier KDIGO guidelines recommended treatment [10], given fruits and vegetables to incorporate into their ad-lib diets had comparable improvement of metabolic acidosis and comparable eGFR preservation [14]. In addition, both alkali treatments decreased three markers of kidney damage, including urinary albumin, NAG, and urine angiotensinogen, a surrogate of kidney AII levels [14]. Supplementation with fruits and vegetables also reduced H^+ retention in individuals with CKD, reduced eGFR, but no metabolic acidosis [35]. Fruits and vegetables prescribed in amounts to provide alkali equivalent to 50% of their calculated dietary H^+ load amounted to adding two to four cups of fruits and vegetables to their daily ad-lib diets [14,35,75]. Participants in these studies were carefully selected to be at very low risk to develop hyperkalemia in response to the increased K^+ load that accompanies fruits and vegetables. Analysis of published data, however, provides little evidence to support that restricting food-based potassium intake in CKD patients prevents hyperkalemia [79]. Nevertheless, clinicians should use caution when considering prescribing fruits and vegetables to CKD patients, particularly those with very low GFR. Other investigators showed that the more that individuals with CKD adhered to a Dietary Approaches to Stop Hypertension diet, one that emphasizes fruits, vegetables, whole grains, and limits red meat, the lower the CKD incidence [80] and the lower the risk of CKD progression to ESKD [81]. Furthermore, such diets appear to reduce mortality in individuals with CKD [82].

Neutralize accumulated H^+ intake: Na^+-based alkali

KDIGO guidelines [10] recommend sodium bicarbonate ($NaHCO_3$) for metabolic acidosis in CKD because it is effective, relatively well tolerated, widely available, and inexpensive. Clinicians prescribe potassium bicarbonate less commonly, except in patients who require substantial HCO_3 replacement (like proximal renal tubular acidosis) in whom HCO_3 administration causes large K^+ losses. Potassium bicarbonate should be avoided in patients with very low GFR (<25% of normal) due to the risk for K^+ retention with hyperkalemia. Because the liver metabolizes citrate to yield HCO_3, clinicians sometimes prescribe Na^+ citrate for patients unable to tolerate $NaHCO_3$. The use of Na^+ citrate is limited by its unpleasant taste, comparatively high expense, and because it promotes gastric aluminum absorption [83]. Consequently, $NaHCO_3$ is the Na^+-based alkali salt upon which we will focus.

Sodium bicarbonate is water soluble and when taken orally rapidly reacts with gastric hydrochloric acid (HCl) to form NaCl, CO_2, and H_2O. Excess HCO_3 that does not neutralize gastric H^+ rapidly empties into the small intestine and is absorbed. Reaction of $NaHCO_3$ with gastric HCl increases gastric lumen pH, stimulating gastric parietal cells to secrete more HCl into the gastric lumen. Secretion of HCl into the gastric lumen leads to HCO_3 extrusion into perigastric capillaries and eventually into the systemic circulation to increase extracellular $[HCO_3]$ if it is reduced. If extracellular $[HCO_3]$ attains a level that exceeds the kidney tubule maximum for reabsorption, excess HCO_3 is eliminated in the urine. Consequently, most individuals without severely reduced eGFR (>25 mL/min/1.73 m^2) can excrete excess HCO_3 and thereby avoid metabolic alkalosis.

Orally administered $NaHCO_3$ at low-to-moderate doses (<0.3 mEq/kg lean body weight daily) has few serious side effects when given to individuals with CKD [84]. Most side effects are due to the release of CO_2 gas after contact with gastric H^+ and include belching, gastric distension, and flatus. Higher doses (>0.5 mEq/kg lean body weight daily) might cause volume retention and possibly exacerbate hypertension and other Na^+-sensitive comorbid conditions in patients with very low GFR (CKD stages 4 and 5). Nevertheless, investigators did not observe a significant difference between the $NaHCO_3$ and control group regarding worsened hypertension requiring higher dose drug therapy as well as worsening edema requiring increased loop diuresis [11]. Others reported no $NaHCO_3$ influence on effects like bloating, flatulence, stomach upset, nausea, edema, shortness of breath, and no patient hospitalizations in patients with CKD and eGFR 15–45 mL/min/1.73 m^2 who received escalating doses of $NaHCO_3$ over 6 weeks [85]. On the other hand, individuals with CKD stages 3 and 4 treated with $NaHCO_3$ required increasing diuretic doses to manage Na^+ retention [86]. Although an increment in oral $NaHCO_3$ caused less Na^+ retention, weight gain, and blood pressure increase than an equal increment of oral NaCl when study participants with creatinine clearance <20 mL/min/1.73 m^2 ate a very NaCl-restricted (10 mmol/day) diet [87], equal $NaHCO_3$ and NaCl increments caused comparable Na^+ retention, weight gain, and blood pressure increase when participants ate a NaCl-containing diet (100 mmol Na^+/day) more commiserate with typical dietary NaCl intake in developed societies [88]. Recognizing that most individuals with CKD have comorbid, Na^+-sensitive states like hypertension that might be exacerbated by the Na^+ accompanying Na^+-based alkali, clinicians should use caution when prescribing Na^+-based alkali to those with CKD and comorbid Na^+-sensitive conditions, particularly when high doses are required to achieve desired outcomes [89].

The optimal daily dose of $NaHCO_3$ that provides kidney and other organ protection yet minimizes side effects remains to be determined. KDIGO guidelines recommend 0.5–1.0 mEq of $NaHCO_3$/kg body weight daily in patients with $PTCO_2 < 22$ mmol/L [10]. Tolerance and compliance of those using $NaHCO_3$ depend on its galenic form. Tablets and capsules are well tolerated and the dose can be better controlled. There is no chemical difference between supermarket baking soda and $NaHCO_3$ powder or tablets in pharmacies but pharmacies can professionally advise individuals regarding interactions, side effects, and warnings. Also, dosing with powdered $NaHCO_3$ is less precise than tablets and its temperature sensitivity makes storage of $NaHCO_3$ challenging. Consequently, the better recommendation for CKD patients is $NaHCO_3$ prescribed and purchased as tablets or capsules from a pharmacy rather a supermarket.

Remove accumulated H^+ intake: H^+-binding polymers

Advances in drug technology include polymers that selectively bind substances in the gastrointestinal tract and remove them from the body with feces. One such polymer selectively binds gastrointestinal HCl and removes it from the body, thereby increasing $PTCO_2$ and doing so as soon as within 24 hours of administration [90]. With continuous use the increase in $PTCO_2$ was sustained over 12 [91] and 52 weeks [92]. Ongoing testing will determine if this and/or other H^+-binding polymers will be approved for treatment of metabolic acidosis and therefore added to the available treatment options.

How might clinicians approach management of H^+ stress, as a kidney protective intervention, in individuals with CKD within the context of the three mechanistic strategies?

Because dietary strategies described improved the most severe end of the spectrum of H^+ stress, that is, metabolic acidosis [14,75], ameliorated H^+ retention in individuals with reduced eGFR but no metabolic acidosis [35], and might prevent metabolic acidosis [31] and H^+ retention [20] in individuals with reduced eGFR, it seems prudent to begin treatment of H^+ stress with interventions that limit dietary H^+ intake and/or include them as adjunctive interventions. Were these dietary strategies alone not to be successful in achieving the treatment goal, it seems reasonable to then recommend H^+ neutralization using Na^+-base alkali as tolerated. Employing this next step of H^+ neutralization only after limiting dietary H^+ intake offers the potential benefit of minimizing the dose of Na^+-base alkali necessary to achieve the treatment goal. If polymer drugs that remove H^+ from the gastrointestinal tract become available for clinical use, it appears reasonable to include them in the armamentarium of drugs used to treat H^+ stress.

Conclusion

The spectrum of H^+ stress appears to contribute to enhanced CKD progression that is increasing ESKD prevalence. Treating H^+ stress by limiting dietary H^+ intake and/or neutralizing accumulated H^+ with food-based and/or Na^+-based alkali appears to be an effective kidney protective strategy. Dietary H^+ reduction treatment of H^+ stress promises to not only provide kidney protection but also to reduce the elevated cardiovascular risk in CKD when accomplished with base-producing foods like fruits and vegetables.

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PART IV

Mineral and vitamin metabolism in kidney disease

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CHAPTER

20

Nutritional management of sodium, chloride, and water in kidney disease and kidney failure

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Introduction

Among all physiologic parameters involved in the homeostasis of human body to maintain what Claude Bernard named the *milieu intérieur* [1], water and sodium balances are probably the mostly tightly regulated. Indeed, in human, multiple mechanisms contribute to maintain sodium and water balance in a narrow range despite large interindividual variations in salt and water intake. These mechanisms include the control of water and salt intake, through behavioral and neuroendocrine pathways, and a precise regulation of sodium and water excretion, mainly through the kidney and its ability to finely tune urinary sodium and water elimination. Thereby, extracellular fluid volume (ECFV), which consists of plasma volume and interstitial fluid volume and represents 25% of body weight, and intracellular fluid volume (ICFV), 33% of body weight, are maintained relatively constant in steady-state conditions. The regulation of ECFV is characterized by the fact that small changes (~2%) in plasma osmolality are sufficient to activate a regulatory response through osmoreceptors, thirst, and vasopressin neurons [2], whereas larger changes in volume (~10%) are necessary to trigger low-pressure baroreceptors and to induce a correction of fluid volumes through fluid intake and a reduction of fluid excretion [3]. Owing to the major role played by the kidney in the regulation of fluid and electrolyte excretion, it is not surprising that alterations in renal glomerular and/or tubular functions, as observed in kidney diseases, have a major impact on the ability to maintain sodium and water balance. In this chapter, we shall discuss water and sodium homeostasis in normal conditions and in chronic kidney disease (CKD) at different levels of glomerular filtration rate (GFR), including end-stage kidney disease (ESKD). We shall also discuss the clinical implications of salt and water excess and the potential benefits of reducing salt intake on renal disease progression and on the occurrence of cardiovascular complications. At last, we shall present the most recent recommendations for water and electrolyte management in CKD.

Regulation of sodium, chloride, and water in healthy conditions

Sodium

Sodium intake is highly variable among human individuals and across populations. Thus in a 2010 survey of sodium consumption around the world, Powles et al. reported sodium intakes ranging between 1.5 and more than 6 g Na/day that would correspond to intakes of salt (sodium chloride) ranging between 3 and more than 15 g/day [4]. The Prospective Urban Rural Epidemiology study reported similar high levels of sodium intake, and these latter were associated with an increased risk of mortality and cardiovascular events [5].

Today, humans on an unrestricted diet ingest sodium in a large excess of the amount needed to maintain fluid and electrolyte homeostasis. Interestingly, in contrast to animals, humans do not have a true appetite for salt [6]. Thus for example, salt depletion does not induce a craving for salt in humans [6]. In fact, the mechanisms responsible for the regulation of sodium intake are multiple and not yet fully understood. Several physiological factors play a role in the modulation of sodium intake

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such as the renin–angiotensin system, aldosterone, the baroreceptor input, and sodium content of the cerebral spinal fluid, which are known to stimulate salt intake in some circumstances [3]. However, cultural as well as environmental and genetic [7] factors are also important determinants of salt intake in populations. Of note, the need for sodium varies during the human life with increased requirements during some periods of growth (children and adolescents) and during pregnancy. The reason why salt consumption is so high today in humans might also be associated with the activation of brain reward pathways [3,8]. Thus one could consider sodium intake per se as a potentially modifiable behavioral risk factor for cardiovascular and renal diseases.

Once ingested, sodium is distributed in the ECFV where it represents the main cation. Sodium balance is maintained essentially by the kidneys, which modulate its excretion through several neurohormonal and tubular ion transport systems, such as the renin–angiotensin–aldosterone system [9,10], the sympathetic nervous system [11], and atrial natriuretic peptides [12], but also prostaglandins [13], endothelin [14], adducing [15], uromodulin [16], and many others.

The mechanisms whereby the kidney maintains sodium balance have been studied essentially in protocols in which individuals are maintained on a low- or high-sodium intake, respectively [17–19]. The renal response to a marked reduction of sodium intake is characterized by an intense reabsorption along the proximal tubule and the loop of Henle, a reabsorption in the distal tubule and a fine-tuning of sodium excretion occurring in the collecting duct mediated by aldosterone [10,18]. In addition, mechanisms linking renal hemodynamics and tubular functions such as the glomerulo-tubular balance and tubule-glomerular feedback contribute to the maintenance of sodium and fluid balance. In healthy subjects, sodium excretion is not regulated by blood pressure (BP). Thus high-salt/low-salt protocols have shown that in healthy subjects, there is no parallel change in BP when salt intake is modified indicating that their BP is salt-resistant as shown in Fig. 20.1. However, this pressure–natriuresis relationship may sometimes differ with parallel changes in sodium intake and BP indicating salt-sensitivity. In that case, BP may be either salt resistant (parallel shift only) or salt sensitive (parallel shift with a flattening of the slope). These patterns are common in elderly, in African American and in individuals with hypertension, diabetes mellitus, and CKD as will be discussed later in this chapter [20]. The high-salt/low-salt crossover studies also demonstrated that although the neurohormonal response is quite rapid, sodium balance and a new steady state are effectively reached only after 3–4 days. With these renal mechanisms of regulation of sodium excretion, a nearly total conservation of sodium may occur in extreme physiological conditions.

This purely "kidney-centric" view of the regulation of sodium and fluid balance was reappraised following the observation of 12 healthy men who participated to flight simulation studies for 105 and 520 days [21]. In these studies, men were submitted to three levels of sodium intake (6, 9, and 12 g NaCl/day) for months and studied in metabolic conditions with multiple hemodynamic, hormonal, and urine measurements during the study. The main observation of these clinical experiments is that despite a constant salt intake urinary sodium excretion varies and there are aldosterone-dependent, weekly rhythms in daily sodium excretion, which result in periodic sodium storage. In addition, there are changes in total-body sodium, which follow longer rhythm periods (monthly or even longer)

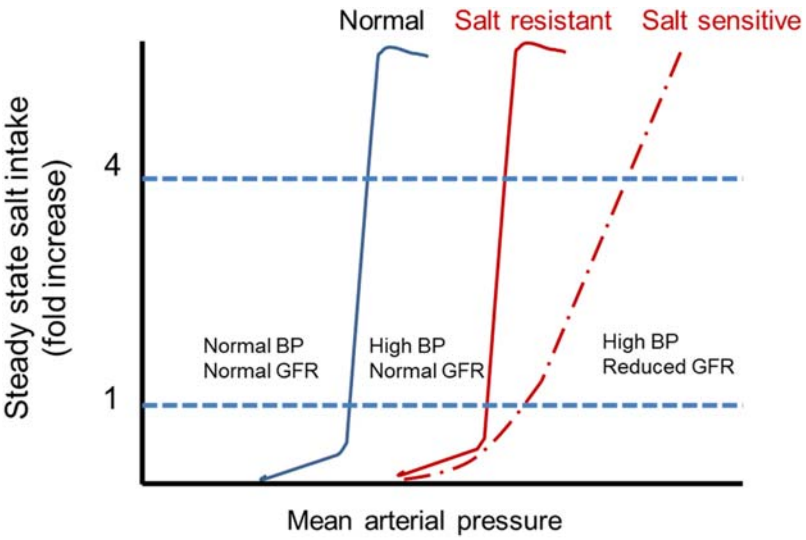

FIGURE 20.1 Illustration of the pressure–natriuresis relationship in normal subjects, in hypertensive patients with a normal renal function and in patients with hypertension and a reduced renal function. Note that hypertensive patients with a normal renal function may also be salt-sensitive. This is common for example in elderly, subjects of African origin, and patients with monogenic forms of hypertension.

without parallel changes in body weight and extracellular water. These latter changes are related to the fluctuations of urinary aldosterone and to cortisol. These findings actually modify the concept of salt balance demonstrating fluctuations in sodium excretion with periods of storage and excretion even in steady state. Moreover, the data support the concept that sodium can be stored in other tissues like skin and muscles [22,23]. Thus the same authors demonstrated using magnetic resonance (^{23}Na-BOLD-MRI) that sodium is actually stored in a nonosmotic way in the skin and muscles in humans [24,25]. Thus even healthy subjects are able to inactivate a substantial proportion of the sodium they receive when infused with hypertonic saline [26]. Glycosaminoglycans have many negative charges enabling the nonosmotic storage of sodium in the interstitium [27]. More recent data have demonstrated the involvement of immune cells, mainly macrophages, in the skin, that sense the hypertonic accumulation of sodium, and activate the tonicity-responsive enhancer-binding protein to initiate expression and secretion of vascular endothelial growth factor C [28,29] (Fig. 20.2). This latter increases electrolyte clearance via cutaneous lymph vessels and increases endothelial nitric oxide synthase expression in blood vessels thereby contributing to the regulation of sodium homeostasis and BP.

These data on new mechanisms involved in the regulation of sodium balance have modified the general concept of two compartments being in equilibrium adding another compartment in which sodium can be stored nonosmotically, thereby participating in the long-term maintenance of sodium balance [30].

Chloride

Chloride is the main anion present in the extracellular compartment. In general, changes in plasma and urinary chloride excretion follow those of sodium and when the variations in chloride are not proportional to those of sodium, they rather reflect alterations in the acid−base status. Chloride is absorbed in the small and large intestine and is secreted abundantly by the stomach. Chloride can accumulate in the skin as well. Precisely 90% of chloride is excreted in the urine and the other 10% are eliminated in stool and sweat. In the early tubular segments of the nephron, chloride is transported through the same transporter systems than sodium but this is not the case in the more distal segments of the nephron where specific chloride transport pathways exist [31,32]. Chloride's main function is to concentrate urine. Indeed, reabsorption of chloride occurs actively in the loop of Henle and this establishes the transport gradient needed for the "countercurrent" urine concentrating mechanism.

Water

As it is the case for sodium intake, fluid intake is highly variable among adult individuals essentially

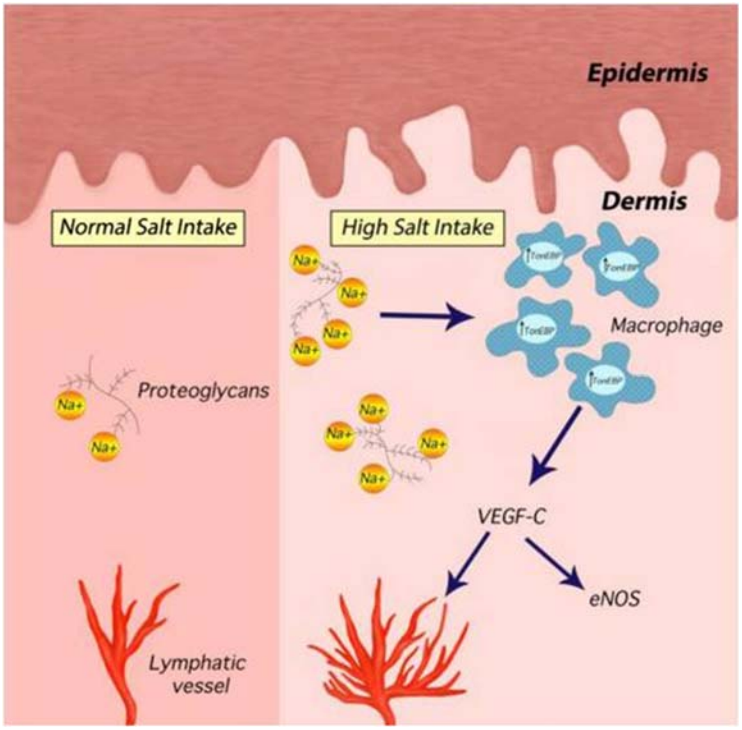

FIGURE 20.2 Skin mechanism for buffering dietary salt. Under normal conditions, Na^+ binds to negatively charged GAGs in the dermal interstitium, without commensurate water, allowing high concentrations of Na^+ to accumulate in the skin. During salt loading the Na^+-binding capacity of GAGs is exceeded and interstitial hypertonicity develops. This leads to an influx of macrophages, which release an osmosensitive transcription factor (TonEBP). This induces the secretion of VEGF-C in an autocrine manner, leading to lymphangiogenesis. The enhanced lymphatic network increases Na^+ transport back into the circulation, for eventual removal by the kidneys, preventing a blood pressure rise with salt loading. *TonEBP*, Tonicity-responsive enhancer-binding protein. *From Selvarajah V, et al. Skin sodium and hypertension: a paradigm shift?. Curr Hypertens Rep 2018;20 (11):94, with permission. Open access, article distributed under the terms of the Creative Commons Attribution 4.0 International License (http://creativecommons.org/license(by/4.0/)).*

due to personal habits and cultural and environmental factors. Using urine output as an indirect marker of fluid intake, several surveys have demonstrated that urinary volume excretion varies enormously within and between individuals [33–35]. In healthy individuals the majority of fluid intake (80%) is ingested through beverages and fluid present in food and a smaller volume (about 300 mL) is produced by the cell metabolism (Table 20.1). Fluid output is regulated by the kidney (about 60% of fluid intake), the skin (about 30%), and fecal losses. The respective contributions of these excretion pathways depend on age, gender, fluid intake, sodium excretion, climate, environment temperature, exercising [34].

Regulatory mechanisms contributing to water balance are essentially those associated with hypovolemia and/or increases in plasma tonicity. Thus the predominant mechanism of regulation is thirst and activation of the vasopressin and renin–angiotensin system, mediated in part by the detection of changes in plasma volume by the low-pressure baroreceptors, located in the superior and inferior vena cava and the atria of the heart. Any change in plasma tonicity and central blood volume will initiate a global response that includes adjustments in thirst and sodium ingestion.

TABLE 20.1 Components of normal daily water balance in the adult.

Water intake	
Source of water	Volume (mL/day)
Ingested as fluid	Variable[a], usually 1000–2000
Ingested as solid food	Usually 800–1000
Production from oxidative metabolism	Usually 200–300
Total	2000–3300
Water output	
Routes of water loss	Volume (mL/day)
Urine	Variable[b], usually 1000–2200
Sweat	Negligible, except in hot environment or after exercising, when several thousand mL can be lost
Stools	100
Skin	450[c]
Resspiratory tract	450
Total	2000–3300

[a] *The amount of water ingested depends on cultural influences as well as serum osmolality.*

[b] *Depends on what is needed to achieve water balance.*

[c] *These are pure water losses. The losses are influenced by humidity and body temperature.*

Vasopressin is the main hormone regulating water excretion through its effects on V2 receptors located in principle cells in the late distal tubule and collecting ducts. Vasopressin secretion is stimulated not only by hypovolemia or a high plasma osmolality but also by angiotensin II, nausea, pain, and many centrally acting drugs. In recent years, experimental developments have evidence new pathways stimulating vasopressin secretion and thirst, one of them being located in the tongue, that is, the acid-sensing taste receptor cells (TRCs) expressing otopetrin 1 on type III presynaptic TRCs [36]. Another observation is the role of the median preoptic nucleus neurons activity, which serves as a central detector to discriminate fluid ingestion from solid ingestion and, hence, promote acute satiation of thirst through the subfornical organ and other downstream targets [36]. This enables to cut the thirst feeling before tonicity or volume balance has actually been restored.

In summary, the human body is extremely well organized to fight against dehydration and minor changes in plasma tonicity. Some systems may seem redundant but are important to maintain the homeostasis of extracellular and ICFVs and protect our organs, mainly the brain, from excessive fluctuations in volume or tonicity.

Regulation of sodium, chloride, and water in kidney diseases (stages 3–5)

Regulation of sodium balance in chronic kidney diseases

Considering the central role of the kidney in maintaining fluid and electrolyte balance as discussed previously, it is not surprising that acute as well as chronic alterations in kidney functions affect its regulatory capacities. Nevertheless, the ability of patients with CKD to maintain salt balance on a regular sodium intake usually remains rather intact until GFR is less than 15 mL/min. Below a GFR of 15 mL/min, kidneys are often unable to increase sodium excretion sufficiently to maintain a satisfactory sodium balance. In that case, salt intake must be reduced to avoid any increase in plasma volume.

In CKD patients, quantitative changes in physiologic factors involved in the maintenance of sodium balance occur. This is the case for aldosterone, the sympathetic nervous system, natriuretic peptides, peritubular physical factors. Thus as the number of nephrons is reduced, sodium excretion per remaining nephron increases, leading to an increase in the fractional excretion of sodium [37], thereby contributing to the so-called magnification process observed in CKD [38]. Thus salt-sensitive hypertension is highly prevalent in CKD stages 3–5 [39]. The elevated BP increases urinary sodium excretion as the pressure–natriuresis relationship is shifted to the right (Fig. 20.1). In addition, nonosmotical storage of sodium in the skin and muscle appears to be greater in patients with CKD, in elderly subjects and in CKD patients receiving hemodialysis when compared to healthy individuals [24,40,41] and this may represent another mechanism protecting CKD patients from sodium overload, volume expansion, and excessive elevation of BP.

In more advanced CKD a salt-wasting state has been described, characterized by an incapacity to lower urinary sodium excretion on a very low-salt diet and leading to a net sodium loss [42]. Therefore these patients are more vulnerable in case of acute sodium depletion. The same holds true for acute volume depletion. However, this does not seem to be the case when sodium depletion is gradual [43]. Taken together, these two observations suggest that the kidneys cannot adjust immediately to marked and acute changes in sodium intake but can adequately adjust to a decrease in sodium intake if these changes occur slowly. This is actually the main characteristic of CKD patients in whom any sudden excess in sodium intake can cause volume expansion, hypertension, and edema whereas sudden decreases in sodium intake can induce volume depletion and aggravation of renal function due to prerenal azotemia.

Of note, the anion accompanying sodium appears to have an important influence on the sodium-wasting phenomenon. Thus renal sodium wasting is accentuated if sodium is ingested as $NaHCO_3$ (sodium bicarbonate) rather than NaCl. This was demonstrated when patients with various forms of CKD were fed a diet in which the source of sodium was either 100 mM/day of NaCl or 100 mM/day of $NaHCO_3$ [44]. During NaCl feeding, patients maintained a satisfactory sodium balance. However, during $NaHCO_3$ feeding, progressive negative sodium balance developed. This suggested a decreased capacity of the kidney to reabsorb sodium, unless sodium is accompanied by an anion that can easily be reabsorbed, such as chloride.

Regulation of water balance in chronic kidney diseases

The limitations in the ability to regulate water excretion in patients with CKD are rather similar to those observed with sodium. An impaired ability to both concentrate and dilute urine is documented in all forms of CKD stages 3–5. It occurs earlier and more severely in primary tubule-interstitial renal diseases compared to primary glomerular diseases. However, in either form of CKD, when GFR falls to less than 20 mL/min in adults, the maximum urine concentration barely exceeds plasma osmolality (300 mOsm/L) and the minimum urine osmolality is approximately 200 mOsm/L. Therefore in advanced kidney disease, an osmolar load of 600 mOsm/day requires a urine output of about 2 L/day. Consequently, urine output is usually higher than normal in advanced kidney disease. It is only when ESKD is reached that urine volume would be expected to be lower than normal regardless of fluid intake.

The impaired renal concentrating ability in CKD is related to tubular dysfunction, changes in medullary structure and tonicity, single-nephron hyperfiltration, and vasopressin resistance. These dysfunctions lead to higher urine volume to excrete the daily osmotic load (600–900 mOsm/day). Thus CKD patients will become dehydrated and hypernatremic if water intake is insufficient. On the other hand, an excessive water intake in advanced CKD may cause volume overload and hyponatremia. Dysnatremia reflecting changes in water intake and excretion have been frequently reported in CKD patients. In a study of the prevalence and incidence of dysnatremia and its associated mortality in 655,493 US veterans with nondialysis-dependent CKD, 13.5% of patients had episodes of hyponatremia (serum Na < 136 mmol/L), and only 2% had hypernatremia (serum Na > 145 mEq/L) [45]. During a median follow-up of 5.5 years, 26% of them had at least one episode of hyponatremia, and 7% had at least one episode of hypernatremia. Management of such patients is problematic if they become severely hyponatremic due to the high mortality risk [45].

Regulation of sodium and water balance in kidney failure (CKD stage 5D)

In patients with ESKD needing a substitution therapy such as hemodialysis or peritoneal dialysis, the lack of renal clearance leads to sodium and water overload and maintaining a balance is a challenge. Thus using bioimpedance spectroscopy, 25%–30% of patients undergoing maintenance hemodialysis or peritoneal dialysis have a fluid overload of more than 2.5 L [46,47] and in one study, only about one-third of patients on hemodialysis had a fluid overload of less than 1.1 L [47]. As discussed earlier, sodium accumulates in tissue in osmotically active (ECV, bones) and inactive forms (skin, muscles, arteries). Recent data have confirmed that sodium accumulation in skin and muscle occurs in hemodialysis patients [40,48] and in a greater magnitude in patients with type 2 diabetes [48]. The tissue accumulation of sodium can be partly removed during hemodialysis sessions [40,48]. In hemodialysis the accumulation of sodium in muscle might have some significant impact on glucose metabolism favoring the development of insulin resistance [49]. Recently, Canaud et al. have elegantly reviewed the impact of these new pathogenic mechanisms controlling sodium and fluid balance in patients on maintenance hemodialysis [50].

Clinical implications of salt and water excesses in kidney diseases

In CKD patients the accumulation of salt and fluid, as well as salt and volume depletion, have important clinical consequences, which will depend on the severity of the kidney impairment. The most frequent complications associated with marked alterations in sodium and fluid balances are the following: (1) development of hypertension, (2) kidney disease progression as reflected by changes in proteinuria and GFR, (3) development of target organ damages such as left ventricular hypertrophy or vascular stiffening, and (4) increased risk of cardiovascular and total mortality.

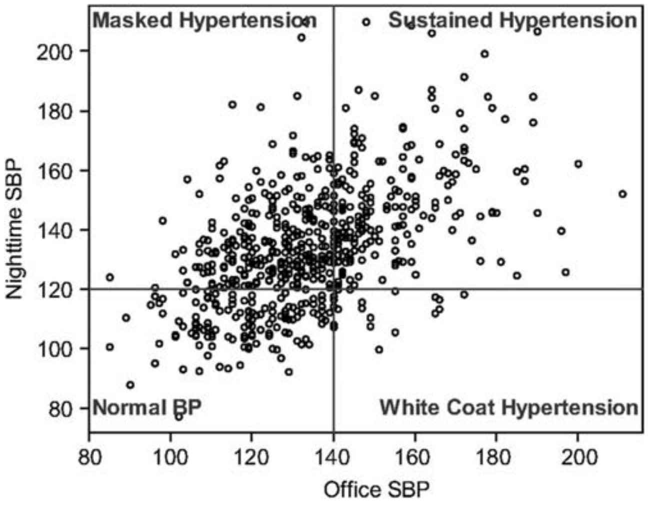

FIGURE 20.3 Comparison of clinic SBP and nighttime ambulatory SBP in 377 participants with controlled blood pressure in the African American Study of Kidney Disease Cohort Study. In this subgroup, 70% had masked hypertension because of elevated nighttime BP. *SBP*, Systolic blood pressure. *From Pogue V, et al. Disparate estimates of hypertension control from ambulatory and clinic blood pressure measurements in hypertensive kidney disease. Hypertension 2009;53 (1):20–7, with permission (free access).*

Stages 3–5

Hypertension

The prevalence of hypertension is high in patients with CKD ranging between 10% and almost 100% depending on the type of renal disease and its severity, as BP increases when renal function is worsening [39]. As discussed earlier in this chapter, most CKD patients have a salt-sensitive form of hypertension associated with an expanded ECFV and a high-sodium intake [51]. According to Guyton's hypothesis, the elevation of arterial BP enables to eliminate sodium and thereby to lower BP. However, this compensatory mechanism may become ineffective in advanced kidney disease. Thus one of the main characteristics of hypertension in CKD is the progressive loss of the dipping pattern of BP profile as GFR declines [52–54]. In one study in 26 CKD patients with glomerular disease and various degrees of kidney impairment, Fukuda et al. showed that the duration of nighttime hypertension increased progressively as renal function deteriorated suggesting that impaired daytime natriuresis leads to a progressive compensatory increase in nocturnal BP to maintain sodium balance [55]. The absence of nocturnal dipping in CKD patients is a particularly important feature as it increases the risk of renal disease progression, cardiovascular events, and mortality [56,57]. It is also the most common cause of uncontrolled masked hypertension in patients with kidney diseases as shown in a post hoc analysis of the African American Study of Kidney Disease and Hypertension Collaborative Research Group [58] (Fig. 20.3). In CKD patients with masked nocturnal hypertension, the prevalence of proteinuria and left ventricular hypertrophy was higher than in patients with well-controlled hypertension [58]. In addition to the abovementioned mechanisms, an excessive sodium intake may affect BP and the cardiovascular system through its direct effects on oxidative stress, inflammation, and endothelial function [59].

Does a reduction of sodium intake lower arterial BP in hypertensive CKD patients? Several small- and middle-size randomized controlled studies have demonstrated that reducing sodium intake lowers BP in CKD patients [60]. Thus in a Cochrane analysis performed in 2015, McMahon et al. found eight randomized controlled trials (RCTs) assessing the effect on BP of two or more levels of salt intake in people with various CKD stages. The study duration ranged between 1 and 26 weeks and the total number of patients was 258. The mean reduction in 24 hours urinary sodium excretion was approximately 105 mmol/24 h and decreases in systolic and diastolic BP were, respectively, −8.75 and −3.70 mmHg [60]. On a low-sodium diet, less antihypertensive drugs were used. In a more recent study, Saran et al. investigated the effects of a low-sodium intake (<2 g Na/day) administered for 4 weeks in a crossover design in 58 patients with CKD stages 3–4. Significant changes in whole-body extracellular volume and calf intracellular volume, urinary sodium excretion, body weight, and 24-hour systolic BP [−10.8 mmHg; 95% confidence interval (CI), −17.0 to −4.6] were observed on the low-salt regimen [61]. The latest metaanalysis by Garofalo et al. reported similar results when combining the results of eleven RCTs and information from 738 patients with CKD stages 1−4 [62]. In an interesting study, Meuleman et al. randomized 138 patients to usual care or usual care plus an intervention comprising education, motivational interviewing, coaching, and self-monitoring of BP and sodium [63]. At 3 months, significant decreases in urinary sodium excretion and both office and ambulatory BP were observed. However, at 6 months, there were no differences in sodium excretion and ambulatory BP in the two groups. These results demonstrate the difficulties to maintain a low-sodium diet in the real life, outside a study protocol as it will be discussed later in this chapter.

Taken together, the data available so far demonstrate that reducing sodium intake in patients with CKD stages 1−4 contributes to lower BP and reduce ECFV.

An excessive sodium intake has also a critical role in the management of hypertension in CKD patients. Indeed, as in hypertensive patients with a normal renal function, a high-sodium intake has been shown to blunt the BP-lowering efficacy of several antihypertensive classes, mainly blockers of the renin−angiotensin system (ACE inhibitors and angiotensin receptor blockers) and diuretics [64]. However, this is not the case for calcium antagonists, which have a natriuretic effect [64,65]. Therefore for these drugs to have their maximal antihypertensive efficacy, it is preferable that patients avoid a high-salt diet. Similarly, drugs inducing a sodium retention such as nonsteroidal antiinflammatory drugs or inhibitors of cyclooxygenase type 2 will reduce the efficacy of the same antihypertensive drug classes and induce a rise in BP particularly in patients with a reduced renal function [66,67]. The recent recommendations for the treatment of hypertension in CKD emphasize the important role of diuretics (thiazides or loop diuretics depending on the CKD stage) in the management of hypertension in patients with a reduced renal function [68,69]. Single pill combinations containing a blocker of the renin−angiotensin system and either a diuretic or a calcium channel blocker are now strongly recommended as first-line therapy, based on the results of recent large randomized clinical trials such as the ACCOMPLISH trial [70].

Overall, the data presented previously emphasize the risk of hypertension associated with a high-salt intake. In contrast, increasing water intake has a modest, if any, effect on BP unless patients have a very advanced CKD. Regarding the impact of salt and water depletion on BP, one has to mention that chronically reducing salt intake down to 2 g Na/day was not associated with orthostatic hypotension or severe hypotension in CKD patients. Yet, acute episodes of salt and water depletion may be associated with hypotension and a transient aggravation of renal function. This is the reason why patients with CKD should remain well hydrated and should avoid rapid and large changes in sodium intake.

Proteinuria

Proteinuria is a recognized marker of kidney disease and of the risk of CKD progression [71,72]. In the general population, proteinuria is strongly associated with the risk of cardiovascular or all-cause death [73]. In most clinical studies having assessed the impact of salt intake on BP, an effect on proteinuria was also observed indicating that patients on the lower sodium diet had lower albuminuria or proteinuria [60,63]. In the 2018 metaanalysis of Garofalo et al. [62], a modest reduction of salt intake was associated with a reduction of albuminuria/proteinuria in patients with CKD stages 1−4. One of the landmark trials is the crossover trial (HONEST) performed by Slagman et al., which included 52 patients with proteinuric CKD (mean protein excretion 1.6 g/day, mean creatinine clearance 70 mL/min), already treated with lisinopril [74]. In this study, patients received four treatments given in random order, each for 6 weeks, that is, a low-sodium diet with placebo, a low-sodium diet with valsartan, a regular-sodium diet with placebo, and a regular-sodium diet with valsartan. Compared with the regular-sodium diet, the low-sodium diet decreased mean daily protein excretion significantly and the reduction in urinary protein excretion was greater than that obtained with the addition of valsartan (51% vs 21%). This observation demonstrates that reducing sodium intake in CKD patients with proteinuria is actually more effective than intensifying the blockade of the renin−angiotensin system to lower proteinuria. Another study has shown that sodium restriction is as effective as adding a diuretic on top of blockers of the renin−angiotensin system to reduce proteinuria [75].

Today, the administration of a blocker of the renin−angiotensin system is recommended as first-line therapy in proteinuric CKD patients with or without hypertension [68,69]. However, in this patient population, one should note that the antiproteinuric effect of blockers of the renin−angiotensin system or nondihydropyridine calcium channel blockers is offset with a high-salt intake, even when BP control seems appropriate, and conversely, the antiproteinuric efficacy of these drug classes is enhanced with salt restriction. Taken together, these data demonstrate sufficient evidence supporting a reduction of sodium intake to decrease proteinuria in CKD.

The role of water intake on proteinuria is less clear, at least in humans. Indeed, in animal studies, an increase in water consumption has been shown to lower BP and proteinuria and improve survival in 5/6 nephrectomized rats [76]. In a recent observational cohort study of 2182 participants aged older than 20 years, there were no differences in urinary protein excretion between those subjects who had a urinary volume greater than 3.5 L/24 h and those with a urine output of less than 2.1 L/24 h [77]. In healthy human subjects the administration of vasopressin has been reported to increase proteinuria [78] but this was not the case in patients with a syndrome of inappropriate antidiuresis [79]. Thus as far as one knows, the impact of a high or low-water intake on urinary protein excretion remains poorly understood and more clinical studies are needed before any recommendation could be made.

Kidney disease progression

Hypertension and proteinuria are two major determinants of kidney diseases progression. Since sodium impacts both parameters, it should have an influence on the rate of decline of renal function in patients with or without CKD. As reviewed by Smyth et al., several small clinical studies reported a more rapid decline in renal function in CKD patients on a high-sodium diet but whether a low-sodium diet actually retards the progression of renal diseases has not been convincingly demonstrated [80]. In non-CKD patients the situation is even more controversial as renal function decline aggravation has been reported in patients on a low-sodium intake suggesting a J-shaped curve relationship between sodium intake and the rate of renal function decline [80]. In a large analysis, Smyth et al. have assessed the relationship between 24 hours urinary sodium excretion and GFR decline of 30% or more or the need for chronic dialysis in the 28,879 high cardiovascular risk patients having participated in the ONTARGET and TRANSCEND trials [81]. The mean follow-up of these patients was 4.5 years. Interestingly, no significant association between urine sodium and any marker of renal disease progression was found whereas positive associations were found with urinary potassium excretion, a higher potassium excretion having a favorable impact on renal outcomes. In the Chronic Renal Insufficiency Cohort Study the prospective analysis of the data of 3939 CKD participants demonstrated that a high urinary sodium and potassium excretion is associated with an increased risk of CKD progression [82]. In a post hoc analysis of the REIN trials, the progression of the decline in GFR was evaluated in 500 CKD patients with nondiabetic nephropathies according to the level of salt excretion [83]. There was a threefold increase in the incidence of ESKD in patients with the highest urinary sodium/creatinine ratio. In addition, the high-salt intake blunted the antiproteinuric effect of ramipril. In a post hoc analysis of the RENAAL and IDNT trials, Lambers Heerspink et al. found that the risk of renal events was significantly reduced by 43%, not changed, or increased by 37% for each tertiles of increased sodium intake. This suggests that a low-sodium intake potentiates the renal protective benefits of blockers of the renin–angiotensin system in CKD patients with type 2 diabetes [84]. Thus in the absence of a specifically designed randomized trial in CKD patients, it is difficult to propose evidence-based recommendations on how much sodium CKD patients should eat to slow down the progression of their kidney disease but some low-level evidence does exist to support sodium restriction.

Whether fluid intake affects the decline in renal function in CKD patients remains controversial. In a community-based study of 2148 subjects with a baseline GFR > 60 mL/min/1.73 m^2, Clark et al. reported that the decline in kidney function was significantly slower in those with the higher (> 3 L/day) versus lower (<1 L/day) urine output in a preliminary feasibility study [85]. However, this finding was not confirmed in the larger trial conducted by the same authors and published in 2018 [86]. In two cross-sectional population-based studies conducted in Australia, a high water intake (> 3.2 L/day), calculated based on a food frequency questionnaire, also appeared to afford renal protection when compared to a low-water intake [87]. However, in a post hoc analysis of the MDRD trial, in which GFR and 24-hour urinary volume were measured at several time points, a high urinary volume was associated with a more rapid decline in renal function and thus in CKD patients with or without polycystic kidney disease (PKD) [88]. Thus the authors recommended letting thirst guide the fluid intake of CKD patients and not to encourage them to drink more. Nevertheless, today, a high water intake belongs to the recommendations for the prevention of CKD progression in some renal diseases such as PKD, although it may be less effective than a vasopressin antagonist [89]. Of note, plasma copeptin levels have been shown to correlate positively with urine osmolality and the development of renal cysts and negatively with estimated GFR in a population-based study [90].

Cardiovascular morbidity and mortality

In patients with CKD a high-sodium intake (above approximately 6 g/day) is associated with a higher risk of having a cardiovascular event, including heart failure, myocardial infarction, and stroke [91]. However, prospective studies are lacking demonstrating that lowering sodium intake actually reduces cardiovascular morbidity and mortality in CKD patients and the possibility of a J-shaped curve cannot be excluded.

Few data are available on the impact of fluid intake on morbidity and mortality in the general population or in CKD patients. In California, Chan et al. reported a lower incidence of coronary events in subjects who had a high daily intake of water (five or more glasses/day) compared with those who had a low daily water intake (two or fewer glasses/day). The relative risks were of 0.46 (95% CI: 0.28, 0.75; P trend = .001) in men ($n = 8200$) and 0.59 (95% CI: 0.36, 0.97) in women ($n = 12{,}017$). In a more recent analysis of NHANES III, Wu et al. found that subjects in the highest quartile of fluid intake had the lowest overall mortality, but cardiovascular mortality was similar across quartiles of fluid intake [77]. However, so far, no prospective RCT supports a recommendation to drink more than 2.5–3 L/day. In any case, these volumes of water are difficult to achieve and maintain by CKD patients and there may be a risk of inducing hyponatremia.

Dialysis

Hypertension

Hypertension is common in CKD stage 5D on hemodialysis or peritoneal dialysis. Indeed, 50%–85% of hemodialysis patients and nearly 30% of peritoneal dialysis patients are hypertensive according to various studies and registries [92–94]. Hypertension is associated with an increased risk of morbidity (left ventricular hypertrophy, coronary heart disease) and mortality in CKD stage 5D [94–97]. One study has shown that increase in BP during hemodialysis is associated with a reduced 2-year survival, particularly in those patients with a relatively low BP at baseline [98]. Fluid overload and chronic salt loading leading to a high interdialytic weight gain belong to the main factors contributing to the development and maintenance of hypertension in patients on hemodialysis [94,99]. As mentioned previously, sodium accumulates in tissues (skin and muscles) of patients treated by hemodialysis and this may contribute to the development of hypertension and other cardio-metabolic complications such as glucose intolerance, left ventricular hypertrophy, malnutrition, and accelerated vascular aging [50]. Hypertension is less frequent in patients on frequent hemodialysis or longer hemodialysis sessions, which enable a better correction of fluid overload and subtraction of sodium excess. In a randomized controlled study in hemodialysis patients, sodium restriction to 2 g/day, compared to the usual diet, was not found to lower BP but reduced significantly the inflammatory profile of patients [100]. However, in another study of 12 patients on peritoneal dialysis and 15 patients on hemodialysis, significant decreases in BP were observed when patients were placed on a strict salt restriction [101]. In a retrospective analysis of 307 patients on peritoneal dialysis, BP was comparable in patients on a low- and high-sodium intake [102].

Cardiovascular morbidity and mortality

In ESKD, sodium and fluid overloads are recognized factors increasing the patients' morbidity and mortality although results are somewhat discordant. Thus in a post hoc analysis of 1770 patients of the Hemodialysis (HEMO) Study, the Cox regression analysis found that higher baseline dietary sodium was independently associated with a greater all-cause mortality [103]. In contrast, the retrospective cohort study in 303 patients on peritoneal dialysis in Japan found the opposite, a low-sodium intake being significantly associated with a higher overall and cardiovascular mortality [102]. However, the results of this latter study might be biased, as sodium intake was associated with higher lean body mass, younger age, and higher BMI. A low-sodium intake may also be associated with a poor nutrition, which, per se, increases mortality in patients on dialysis.

Results are more consistent when assessing the impact of fluid overload on morbidity and mortality. In the international cohort study in 8883 hemodialysis patients from the European MONDO database, fluid overload was found to be a significant risk factor for short-term mortality and the impact of fluid overload on mortality was even greater when combined with the patients' inflammatory status [47]. Several other studies have confirmed the associations of fluid overload with mortality but also between fluid overload and left ventricular hypertrophy, endothelial dysfunction, inflammation, and malnutrition [104–108].

Recommendations for the nutritional management of sodium, chloride, and water

Determination of sodium intake and water balance

The management of salt and fluid intake should start with the identification of the amount of sodium and fluid ingested by patients, and this is challenging. Indeed, the recommended method to assess sodium and fluid intake in clinical practice is the collection of urine over 24 hours. This method, which assumes that the patient has a stable salt intake and that the urine output reflects the oral intake, is known to have some limitations such as incomplete collection and reluctance of patients to repeat the procedure. The recent work of Titze's group has added other limits to 24 hours urine collections demonstrating that 10%–15%, and perhaps more, of the ingested salt is actually stored in tissues and hence not recovered in the 24 hours urine [21,24,109].

Based on their observations of substantial variability of sodium excretion despite a fixed intake, they now recommend performing several 24 hours urine collections to have a more detailed assessment of sodium intake. However, this is hardly feasible in clinical practice. For that reason the measurement of sodium excretion in single 24 hours urine collections will probably remain the gold standard in every day practice. Frequency food questionnaires might help in some circumstances, but other health-care professionals than physicians should perform them, because it is time-consuming.

The development of ^{23}Na-MRI is an interesting new approach to evaluate how much sodium and water have accumulated in tissues. This technique might become useful to manage CKD patients, in particular those on maintenance dialysis [50]. However, so far, this costly approach remains in the field of clinical research and more data are needed to validate its clinical potential in preventing target organ damage and eventually mortality in patients with hypertension and/or kidney disease. Today, several research programs combining different renal functional MRI techniques to measure renal flow, tissue oxygenation, or tissue fibrosis are under clinical investigations to improve the global management of CKD patients [110].

The clinical assessment of fluid overload is particularly important in patients on maintenance dialysis although an excess of fluid can be problematic already in patients with earlier CKD stages. In hemodialysis the assessment of fluid overload is essential to determine the “dry weight” of patients, this latter being an important determinant of BP and cardiovascular complications such as left ventricular hypertrophy [50,111,112]. Today, several techniques are available to estimate ECFV. This includes ultrasound of the inferior vena cava or of the lung to assess water accumulation in the interlobular septa of the lung, the use of volume sensors, and mainly the multifrequency bioimpedance spectroscopy, which is an easy-to-use and affordable technique to monitor fluid status and its changes as recently reviewed by Canaud et al. [50].

Recommendations for sodium and fluid intake according to international societies

Recommendations for salt intake have been published for the general population, for patients with hypertension, diabetes, heart failure, and specifically for patients with CKD stages 1–5D. The targets proposed by the different societies and their justifications are summarized in Table 20.2. Of note, since most randomized controlled studies in CKD defined the low low-sodium sodium arm as a sodium intake below 80–100 mmol/day, that is, a sodium intake of less than 2–2.3 g Na/day, it is not possible to evaluate whether lower levels of sodium intake are actually more or eventually less beneficial for CKD patients.

In the general population the recommended salt intake is <2.0 g Na/day (or <5 g NaCl/day) according to the World Health Organization [113] and <2.3 g Na/day (or >5.75 g NaCl/day) according to the 2010 Dietary Guidelines for Americans and the American Heart Association (AHA) [114]. However, the pertinence of this target was challenged by the National Academies of Sciences, Engineering, and Medicine (NASEM, former Institute of Medicine) [118]. Yet, in 2019, a low threshold at <1.5 g Na/day was proposed by this institution for adults older than 18 years with no difference between men and women except during pregnancy [115,118].

For patients with hypertension, European guidelines from the European Society of Cardiology and European Society of Hypertension recommend a sodium intake of <2.0 g Na/day or less than 5 g of salt per day [68]. In the United States the recent AHA and American College of Cardiology guidelines and the US Department of Agriculture recommendations propose a sodium consumption of less than 1.5 g Na/day (3.75 g NaCl/day) in patients with hypertension or a reduction of the usual sodium intake by at least 1 g Na/day [69]. Of note, in chronic diseases, including hypertension, diabetes, and CKD, the NASEM proposed a sodium intake of 2.3 g Na/day [115].

In the nephrology community the 2012 recommendations made by the Kidney Disease: Improving Global Outcomes group were <2 g Na/day (>5.75 g NaCl/day) and those of the K/DOQI group were of <2.4 g Na/day for nondialyzed patients and <2.0 g Na/day for patients on maintenance dialysis [116,117]. In the 2019 update of the Clinical Practice Guideline for Nutrition in CKD, the recommendations are to limit sodium intake to less than 100 mmol/day (or <2.3 g Na/day) to reduce BP and improve volume control in CKD stages 3–5 (nondialyzed) (level of evidence 1B) and patients on dialysis (1C). The main target is to lower BP and to reduce proteinuria in CKD stages 3–5 patients and to better control weight gain and volume control in patients on maintenance hemodialysis (CKD stage 5D) (Prof. Kopple, personal communication).

Therefore the actual recommendations tend to support an apparent consensus to limit sodium intake between 2 and 2.3 g Na/day or 5 and 6 g NaCl/day. The only stricter recommendation is coming from the United States regarding the general population and the management of hypertensive patients with a target of 1.5 g of sodium or 3.75 g NaCl/day. In patients with CKDs, one has to emphasize that some patients actually need a higher salt intake (>7 g NaCl 24 hours) because of the characteristics of their kidney diseases, which promote salt excretion

TABLE 20.2 International recommendations of sodium intake for the general population, hypertensive patients, and chronic kidney disease (CKD) patients.

	Sodium (g/day)	Sodium (mmol/day)	NaCl (g/day)	Justification
General population				
World Health Organization [113]	<2.0	<90	<5	Prevention of hypertension Prevention of cardiovascular diseases
AHA [114]	<2.3	<100	<6	
NASEM 2019 [115]	<1.5	<65	<3.75	
Hypertension				
ESC/ESH guidelines 2018 [68]	<2.0	<90	<5	Reduction of blood pressure
AHA/ACC guidelines 2017 [69]	<1.5	<65	<3.75	Prevention of target organ damages
NASEM 2019 [115]	<2.3	<100	<6	Prevention of cardiovascular diseases
CKD				
K/DOQI—nondialysis [116]	<2.4	<105	<6	Reduction of blood pressure Reduction of proteinuria Retarding CKD progression (e)
K/DOQI—dialysis [116]	<2.0	<90	<5	Reduction of blood pressure Improve volume control
KDIGO 2012 [117]	<2.0	<90	<5	Reduction of blood pressure Reduction of proteinuria Retarding CKD progression (e)
CPGs nutrition nondialysis	<2.3	<100	<6	Reduction of blood pressure Reduction of proteinuria
CPGs nutrition dialysis	<2.3	<100	<6	Reduction of blood pressure Improve volume control

CPGs nutrition guidelines are on the way to be published. *AHA/ACC*, American Heart Association/American College of Cardiology; *ESC/ESH*, European Society of Cardiology/European Society of Hypertension; *KDIGO*, Kidney Disease: Improving Global Outcomes.
e = uncertain evidence.

and induce sodium depletion and hypovolemia if not compensated. This is the case, for example, of patients with medullary cystic disease, Fanconi's syndrome, or hypercalcemia-associated renal impairment.

Regarding water consumption, recommendations are much wider and depend on several external factors such as climate, physical activity, and dietary content of water. The recommendations for the general population differ substantially between the United States and Europe with a total daily fluid intake of 2.7 and 3.7 L/day for women and men, respectively, in the United States and 2–2.5 L in Europe [119]. In CKD patients, there are no clear recommendations except for patients with kidney stone diseases or PKD who are encouraged to drink more than 3 L daily, the higher being the better [120]. A high fluid intake may also help preventing urinary tract infections [121]. However, in the study by Clark et al., patients with a urine output >3.7 L had the best prognosis in terms of kidney disease progression as discussed earlier [85] although in a larger prospective trial, the same authors found that increasing fluid intake by 0.6 L did not affect CKD progression in patients with CKD stage 3 [86]. Thus some authors advocate that fluid intake should just follow thirst, avoiding an excess of sugar-containing drinks. Avoiding a daily oral fluid intake below 1.5 L is probably a reasonable recommendation in CKD patients.

The challenges of reducing salt intake and increasing fluid intake

In prospective interventional trials, interventions to lower salt intake were of relatively short duration (from 2 weeks to 3 months) and were applied using a strictly controlled protocol. The application of guidelines is much more difficult when the restriction has to be maintained for years. Indeed, nonadherence to nutritional recommendations is quite common due to numerous reasons, including a lack of motivation and knowledge, the absence of positive feedback, and the social conditions of patients. Studies have actually demonstrated that, even with the help of nurses practitioners [122,123], cooking sessions [124] or education, and self-management interventions [63], there are quasi no long-term changes in lifestyle in CKD patients. Thus in Meuleman's study, 24 hours urinary sodium excretion decreased by 30.3 mmol/24 h at 3 months from a baseline of 159 mmol/24 h but was back to baseline (157 mmol/24 h) at 6 months [63].

In fact, one has to acknowledge that the effort asked to CKD patients is relatively important. Indeed, sodium intake in the US population averages 3.4 g Na/day (8.5 g NaCl/day) and surveys in CKD populations have shown an average sodium intake clearly above 9 g NaCl/day in most countries, meaning that patients should reduce their salt intake by about 3.5–4.5 g NaCl/day [63,64,123,125–127]. To achieve such targets the implementation of the new recommendations on sodium intake in patients with kidney diseases and kidney failure should be accompanied by practical information, which guide patients in their efforts to achieve the recommended target. The changes should be introduced step by step and practical tips should be provided (Table 20.3) [129]. An excellent example is given by D'Alessandro et al. who published practical tips for the nutritional management of CKD patients in Italy [128] (Fig. 20.4). In patients on maintenance hemodialysis, in addition to reducing salt intake

TABLE 20.3 Tips to reach the desired sodium target in daily life.

1. Move the salt shaker away from the table
2. Cook pasta, rice, and cereals without salt (add in smaller amount directly on cooked food)
3. Use spices (e.g., herbs, lemon, vinegar, hot, pepper) instead of salt or salt-containing condiments (e.g., ketchup, mayonnaise, mustard, barbecue sauce)
4. Look for the amount of sodium on food labels
5. Choose fresh or plain frozen foods and low-salt bread
6. Cut back on frozen dinners, canned soups, packaged mixes, cured meat, and fish (e.g., ham, bacon, anchovies, salmon)
7. Choose fresh (e.g., mozzarella) rather than seasoned cheese
8. Rinse canned foods (e.g., tuna) to remove some sodium
9. Abolish salty snack foods (e.g., chips, nuts)
10. Consume 4–5 servings per day of fruits or vegetables

Adapted from D'Alessandro C, et al. "Dietaly": practical issues for the nutritional management of CKD patients in Italy. BMC Nephrol 2016;17(1):102, with permission.

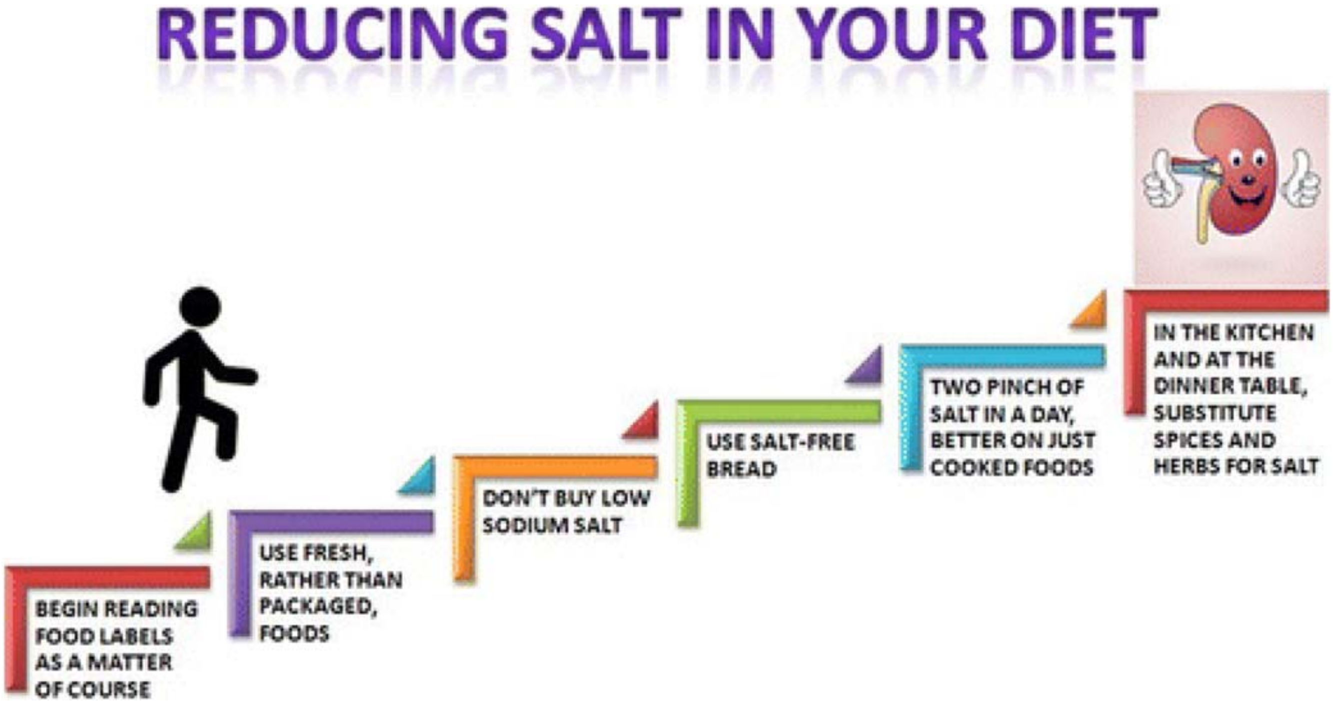
REDUCING SALT IN YOUR DIET
BEGIN READING FOOD LABELS AS A MATTER OF COURSE
USE FRESH, RATHER THAN PACKAGED, FOODS
DON'T BUY LOW SODIUM SALT
USE SALT-FREE BREAD
TWO PINCH OF SALT IN A DAY, BETTER ON JUST COOKED FOODS
IN THE KITCHEN AND AT THE DINNER TABLE, SUBSTITUTE SPICES AND HERBS FOR SALT

FIGURE 20.4 Example of step by step visual tool to reduce salt intake. *From D'Alessandro C, et al. "Dietaly": practical issues for the nutritional management of CKD patients in Italy. BMC Nephrol 2016;17(1):102, with permission. Open access, article distributed under the terms of the Creative Commons CCBY License.*

and increasing sodium clearance during dialysis, other more enjoyable procedures may help subtracting sodium from tissues such as increasing perspiration through the skin using hot water baths or Hamman sessions [130].

Conclusion

Reviews, metaanalyses, and guidelines on fluid and/or sodium intake in patients with kidney diseases or kidney failure, generally, conclude that the level of evidence is weak. The main reasons for this conclusion are that data on hard endpoints such as total or cardiovascular mortality and renal disease progression come mainly from observational studies or post hoc analyses and not from solid prospective RCTs. This is indeed the case, but is not a sufficient reason not to intervene on sodium intake because there are stronger evidence demonstrating that CKD patients can benefit from reducing their salt intake. Thus on a low-salt diet, patients with CKD stages 3–5 have a lower BP, a lower degree of inflammation, less proteinuria, and less target organ damages. Moreover, they need less antihypertensive drugs to control their BP and their progression toward ESKD may be retarded. In patients on maintenance dialysis, a lower sodium and fluid intake is associated with less interdialytic weight gain, less target organ damages, less thirst, a reduced need for antihypertensive drugs, and a better tolerance of hemodialysis sessions. Altogether, these favorable impacts of reducing sodium intake should contribute to improve the quality of life of patients with CKDs.

However, sodium and water should not be considered independent factors without considering other electrolytes and nutritional factors. Thus the interaction between sodium and potassium appears to be very important to prevent cardiovascular events in CKD. In early stages of renal diseases, potassium intake should be sufficient because potassium has been shown to blunt the effects of a high-sodium intake on BP and cardiac complications [131] and may retard GFR decline [132]. Moreover, recent data suggest that the urinary Na/K ratio is a predictive factor for kidney function decline in the general population [133] as well as in patients with early CKD stages [134]. In more advanced CKD stages (3b–5), however, patients should become more careful with their potassium intake because of the risk of hyperkalemia and increased mortality rate.

Sodium intake should also be considered in the context of the overall nutritional status of CKD patients. Physicians should carefully check that sodium restriction does not lead to wasting by reducing food taste and hence appetite, as it occurs in elderly patients on maintenance hemodialysis.

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CHAPTER

21

Management of potassium in chronic kidney disease and acute kidney injury

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Potassium is a key component of the electrochemical system that drives many cellular processes in the body. The distribution of potassium between the intracellular and extracellular fluid compartments, referred to as the *internal potassium balance*, is tightly controlled by adjusting potassium ion channels in the plasma membrane. Under basal conditions, potassium has a steep intracellular: extracellular concentration gradient of approximately 35:1 (Table 21.1), which is maintained by the sodium–potassium ATPase (Na^+–K^+ pump). Of the 45 mEq (1760 mg)/kg of potassium in the body, about 98% is stored intracellularly [1]. As the main intracellular cation, potassium is particularly important in establishing the membrane potential required for action potentials in neurons and muscle cells.

Loss of kidney function, medications, and dialysis can disrupt potassium balance in people with chronic kidney disease (CKD) or acute kidney injury (AKI), causing serious, and sometimes fatal potassium disorders. Because the extracellular fluid compartment has a relatively low volume and potassium concentration, the potassium concentration gradient is far more sensitive to shifts in extracellular potassium concentrations (Table 21.1). As a result, potassium disorders are driven and defined based on serum potassium concentrations.

Kidney disease may be associated with both low and high serum potassium concentrations [2]. In hyperkalemia the higher-than-normal extracellular potassium concentration reduces the potassium concentration gradient and resting transmembrane potential of contractile cells. The resultant effects on action potential generation are responsible for the muscular and cardiac complications associated with hyperkalemia. Hypokalemia has the opposite effect on resting membrane transmembrane potentials but has similar negative effects of muscular and cardiac function.

Potassium balance in health

External potassium balance

Total body potassium content is determined by the difference in potassium inputs and outputs, known as the *external potassium balance*. The primary source of body potassium is diet, and the main routes of potassium loss and excretion are stool, sweat, and urine. In healthy adults, dietary potassium intakes greatly exceed losses in stool and sweat, and external potassium balance is maintained by adjusting potassium excretion in urine.

Dietary intake of potassium in the United States and Canada is typically in the range of 1500–3500 mg/day. Potassium in food is either in the free, ionized form, or bound to small organic or inorganic anions. These latter potassium salts dissociate in the digestive tract, and the majority of dietary potassium is rapidly absorbed in the proximal small intestine via unregulated passive mechanisms, primarily paracellular diffusion, and solvent drag, which are nonsaturated across normal dietary intake levels [3,4].

Unabsorbed dietary potassium is excreted in stool. The overall amount potassium excreted in stool depends on dietary potassium and fiber intakes. When consuming a low-fiber diet, 10%–15% of dietary potassium intake is excreted in stool [5]. As dietary fiber intake increases, stool potassium excretion increases

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TABLE 21.1 Effects of intracellular fluid (ICF) and extracellular fluid (ECF) potassium on the potassium gradient.

	ICF	ECF	ICF:ECF
Volume	28 L	14 L	2:1
Normal [K^+]	140 mEq/L	4 mEq/L	35:1
+20 mmol K^+ (ICF)	141 mEq/L	4 mEq/L	35:1
+20 mmol K^+ (ECF)	140 mEq/L	5.4 mEq/L	26:1

20 mmol $K^+ \approx$ 780 mg (moderate potassium meal).

roughly in proportion to increases in stool output (400–500 mg/100 g stool) and can account for up to a third of potassium output [5]. In a controlled feeding study in young men, average potassium excretion in stool increased by 25 mg for every 1 g of whole grain fiber added to the diet [5]. It is unclear whether the increase in fecal potassium excretion caused by dietary fiber is due to reduced absorption in the small intestines, increased secretion in the large intestines, or a combination of both.

Potassium losses in sweat are generally small (<500 mg/day) and largely unrelated to potassium intake [6]. Exercise and heat exposure can increase potassium losses in sweat substantially, and under extreme conditions, sweating can contribute to potassium depletion [7]. However, the effects are typically transient, as adaptation to exercise and acclimation to heat reduce potassium losses in sweat back to near-normal levels [7].

The kidneys are responsible for excreting excess dietary potassium to maintain external potassium balance. Every day, the kidneys filter and reabsorb approximately 25–30 g of potassium from plasma. Although the majority of potassium is reabsorbed in the proximal segments of the nephron, urinary potassium excretion is fine tuned to maintain external potassium balance by controlling the rate of potassium secretion in the distal convoluted tubules and collecting ducts [8]. This system is highly adaptive and robust, being able to adjust potassium excretion from almost zero to more than 10 g/day [9].

Potassium secretion in the distal nephron is determined by (1) the presence and activity of potassium ion transport proteins, and (2) the electrochemical gradient for potassium [8].

Although the mechanisms involved in potassium secretion have been identified (Table 21.2), the pathways involved in sensing changes in dietary potassium intakes remain unknown. Because urinary potassium excretion rates adapt to match dietary potassium intakes without changes in serum potassium concentrations, an as-yet unidentified feed-forward signaling pathway originating from the gastrointestinal (GI) system has been proposed [10].

If serum potassium concentrations become abnormal, feedback mechanisms become activated to help maintain potassium homeostasis. In addition to the direct effect of serum potassium concentrations on potassium's electrochemical gradient [11], serum potassium directly, and via aldosterone-mediated pathways, adjusts the activity of potassium ion transporters, and the delivery of sodium and water to the distal nephron [12]. Despite their overlapping regulatory mechanisms, renal handling of sodium and fluid is decoupled from potassium such that potassium excretion by the kidneys is largely unaffected by sodium and fluid status (referred to as the "aldosterone paradox") [8].

Internal potassium balance

Internal potassium balance represents the potassium concentration gradient that is central to potassium-related functions and disorders. This balance is regulated by modifying the presence and activity of potassium ion transporters in the plasma membrane of cells, particularly the Na^+-K^+ pumps. Several factors have been shown to impact the internal distribution of potassium, including insulin, catecholamines, acid–base balance and serum osmolality.

The typical meal contains enough potassium to raise serum potassium concentrations by approximately 1–2 mEq/L (Table 21.1). And yet, in healthy individuals, serum potassium concentrations remain relatively stable postprandially due to insulin-mediated increases in Na^+-K^+ pump activity that drives potassium intracellularly [13]. High-potassium foods tend to be rich in glucose and/or amino acids, which stimulate insulin secretion. However, when potassium is consumed without an insulin response, as seen with potassium supplements or untreated insulin-dependent diabetes mellitus, potassium accumulates in the extracellular compartment until the kidneys can excrete it [13].

Postprandial potassium clearance is dependent on insulin, and, therefore, insulin-stimulating macronutrients. However, the pathways involved are primarily

TABLE 21.2 Determinants of potassium secretion and reabsorption in the distal nephron.

Promotes secretion (excretion)	Mechanisms	Promotes reabsorption (retention)
High serum [K^+]	Increases potassium gradient; activates potassium transporters	Low serum [K^+]
High luminal [Na^+]	Sodium reabsorption increases lumen electronegativity	Low luminal [Na^+]
High LFR	Dilutes luminal potassium; activates potassium transporters	Low LFR
High aldosterone	Activates potassium transporters	Low aldosterone

LFR, Luminal flow rate.

TABLE 21.3 Conditions and treatments affecting potassium balance in people with kidney disease.

Decrease serum [K^+]	Increase serum [K^+]
Conditions	
Metabolic alkalosis	Reduced glomerular filtration
Diarrhea and vomiting	Metabolic acidosis
	Diabetes mellitus, insulin resistance
	Hyporeninemic hypoaldosteronism
	Renal tubular acidosis
	Tissue catabolism (e.g., rhabdomyolysis)
Treatments	
Insulin and insulin-stimulating agents	RAAS inhibitors
Thiazide diuretics	K-sparing diuretics
Loop diuretics	β-Blockers
Dialysis	Heparin

RAAS, Renin–angiotensin–aldosterone system.

regulated by potassium intake and are unaffected by conditions of insulin resistance affecting macronutrient metabolism (e.g., type 2 diabetes mellitus) [14]. Instead, in a process called *adaptation*, insulin-mediated potassium uptake by cells adjusts to match usual potassium intake, so that potassium clearance is reduced when following a low-potassium diet and increased when following a high-potassium diet [14,15]. Although the exact mechanisms involved in potassium adaptation are poorly understood, the process appears to involve an aldosterone-dependent increase in the $Na^+–K^+$ pumps [15,16].

In the postabsorptive state, insulin concentrations return to normal, and potassium is released from cells to maintain serum potassium concentrations. In this regard, cells serve as a secondary compartment for temporary storing ingested potassium until the kidneys can excrete it. Prolonged depletion of potassium, as occurs in starvation, results in a decrease in intracellular potassium concentration, which helps drive the rapid decrease in serum potassium concentrations seen in refeeding syndrome [17].

Catecholamines, epinephrine and norepinephrine, also affect internal potassium balance by altering $Na^+–K^+$ pump activity. β_2-Adrenergic receptor binding increases $Na^+–K^+$ pump activity, whereas α-adrenergic receptor binding decreases it. This regulation is thought to help moderate potassium leak from muscle cells caused by contraction [8]. Prolonged physical activity has been shown to increase the number of $Na^+–K^+$ pumps in muscle cells, but it is unclear whether this impacts postprandial potassium clearance, or internal potassium balance [18].

Potassium balance in kidney disease

Patients with kidney disease experience a variety of disturbances in potassium homeostasis and balance that can lead to hypo- or hyperkalemia (Table 21.3,

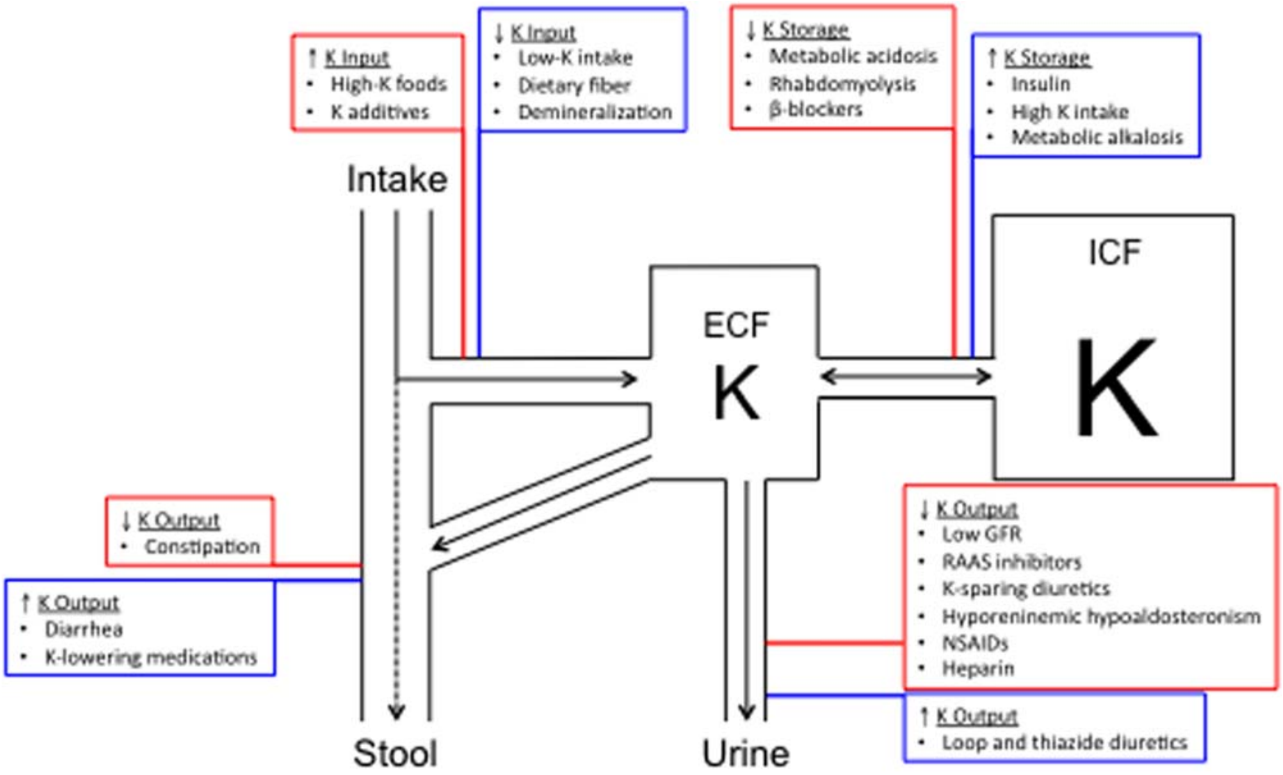
↑ K Input
• High-K foods
• K additives
↓ K Input
• Low-K intake
• Dietary fiber
• Demineralization
↓ K Storage
• Metabolic acidosis
• Rhabdomyolysis
• β-blockers
↑ K Storage
• Insulin
• High K intake
• Metabolic alkalosis
Intake
ICF
K
ECF
K
↓ K Output
• Constipation
↑ K Output
• Diarrhea
• K-lowering medications
↓ K Output
• Low GFR
• RAAS inhibitors
• K-sparing diuretics
• Hyporeninemic hypoaldosteronism
• NSAIDs
• Heparin
↑ K Output
• Loop and thiazide diuretics
Stool
Urine

FIGURE 21.1 Factors affecting potassium balance in people with kidney disease.

Fig. 21.1). Many of these disturbances are direct or indirect results of kidney dysfunction. However, patients with kidney disease tend to have comorbidities and receive medical treatments that contribute to these disorders.

The major disturbance associated with kidney disease, which is generally the primary proximate cause of hyperkalemia, is impaired excretion of potassium by the kidneys. Although the majority of patients with kidney disease are able to maintain external potassium balance at glomerular filtration as low as $15\ \mathrm{mL/min/1.73\ m^2}$, impaired dietary potassium tolerance resulting in postprandial hyperkalemia occurs well before this point [19]. Once glomerular filtration falls below $15\ \mathrm{mL/min/1.73\ m^2}$, maintenance of external potassium balance shifts from the kidneys to the GI tract [20]. The extent of this shift varies considerably between individuals but may reach up to 75% of dietary potassium intake (>3000 mg/day) in some individuals [21]. The increase in potassium excretion in stool is mediated by BK channels on colonic epithelial cells that secrete potassium into the large intestine [20]. Due to the dependence on the GI tract for maintaining potassium excretion, constipation has been proposed as a modifiable risk factor for hyperkalemia in people with advanced kidney disease [22].

Even among people with kidney disease who have adequate glomerular filtration, potassium excretion in the kidneys is often hindered by factors affecting potassium secretion in the distal nephron. These factors typically involve impaired aldosterone signaling (Table 21.3, Fig. 21.1). Aldosterone secretion may be inhibited, as in hyporeninemic hypoaldosteronism secondary to diabetes mellitus or tubulointerstitial diseases, or treatment with renin–angiotensin–aldosterone system (RAAS) inhibitors such as angiotensin converting enzyme-inhibitors and angiotensin II receptor blockers [23]. Alternatively, aldosterone response may be impaired, as in type IV renal tubular acidosis, or treatment with potassium-sparing diuretics [23].

Although impaired potassium excretion is the norm in kidney disease, excess potassium excretion can also occur through several routes and lead to hypokalemia. In the kidneys, potassium-depleting diuretics used to treat hypertension and fluid overload, including thiazide and loop diuretics, increase potassium secretion by delivering more sodium and fluid to the distal nephron [24]. Potassium can also be lost via the GI tract in patients with diarrhea, which has many potential causes in this population (e.g., infections, phosphate binders) [24,25]. In end-stage kidney disease, dialysis becomes another means of removing potassium from the body. However, it is possible to remove potassium too rapidly, or with longer dialysis treatments such as long-dwelling peritoneal dialysis and continuous renal replacement therapy, to remove too much potassium.

People with kidney disease may also have disturbances in internal potassium balance that contribute to potassium disorders. As the primary regulator of internal potassium balance, Na^+-K^+ pumps are often involved. Medications and treatments that inhibit Na^+-K^+ pumps such as β-blockers promote potassium efflux, whereas those that activate Na^+-K^+ pumps such as insulin promote potassium influx. Insulin release in response to dialysate glucose is thought to contribute to the high rates of hypokalemia seen in patients treated with peritoneal dialysis. Of interest, although insulin-mediated potassium clearance is normal in people with kidney disease, insulin resistance and type 2 diabetes mellitus are associated with hyperkalemia. This may be partly due to hyperglycemia, as high serum osmolality draws fluid from cells, encouraging potassium efflux through solvent drag, and raising the potassium concentration gradient.

Another major cause of abnormal internal potassium balance in people with kidney disease is metabolic acidosis. In healthy individuals the kidneys help regulate acid−base balance by modifying hydrogen ion excretion, and bicarbonate ion reabsorption. As such, mild−moderate metabolic acidosis often occurs in people with kidney disease [26]. During metabolic acidosis, particularly mineral acid metabolic acidosis, extracellular hydrogen ions are indirectly "exchanged" for intracellular potassium ions, reducing acidosis, but raising serum potassium concentrations [8].

Assessing potassium disorders

Managing potassium disorders begins with a thorough assessment of their presentation and potential causes. The systems regulating potassium homeostasis are robust, as to prevent life-threatening shifts in serum potassium concentrations. Consequently, potassium disorders generally result from the combination of multiple factors affecting internal and external potassium balance. As diet can modify these processes in numerous ways, an individualized, etiology-based approach is best for managing these conditions.

Serum potassium concentrations are greatly influenced by recent exposures, so dietary assessment should start with a recall of foods and beverages consumed in the day of the abnormal blood test. This recall should be paired with a diet and medical history to probe for notable changes in the previous weeks. Although hyperkalemia can sometimes be attributed to specific, high-potassium foods and beverages (Table 21.4), the amount of potassium needed to cause a clinically relevant increase in serum potassium concentrations generally exceeds that found in standard portion sizes, unless potassium clearance is severely impaired [13].

For chronic management a detailed 3-day food record should be used to evaluate usual dietary intake. Food records are preferable to dietary recalls for assessing potassium intake, as critical details of food processing and preparation can more easily be captured when recorded in real time rather than recalled from memory. Key factors to consider when analyzing food records are reflected in Table 21.5 and should expand beyond food choices to include how foods and beverages are combined in meals and distributed throughout the day.

A 24-hour urine potassium can be a useful adjunct to dietary assessment of potassium disorders. In non-dialyzed patients with preserved potassium excretion by the kidneys, urine potassium output should be approximately 70%−90% of potassium intake, providing an objective estimate of potassium exposure for assessing, monitoring, and evaluating potassium intake. Urine potassium outputs that differ substantially from expected, based on food records and serum potassium concentration, indicates a central kidney component to the disorder. Potassium wasting or impaired potassium excretion by the kidneys should be suspected if urine potassium output is >30 mEq/d (>1000 mg) in hypokalemia or <65 mEq/d (<2500 mg) in hyperkalemia, respectively.

TABLE 21.4 Lists of low- and high-potassium foods across food groups.

Food group	Low potassium	High potassium
Fruit	Apples, grapes, strawberries, and watermelon	Bananas, kiwi fruit, avocados, oranges, and cantaloupe
Vegetables	Cucumber, green beans, and bell peppers	Potatoes, tomatoes, squash, and spinach
Grains	Most grains	
Dairy	Cheese	Milk, soymilk, and yogurt
Protein	Eggs, beef, pork, and poultry	Nuts, seeds, legumes, and fish
Other		Coffee and tea

TABLE 21.5 General dietary strategies for preventing and managing hyperkalemia in people with kidney disease.

Strategy	Rationale and considerations
1. Eat balanced meals and snacks (i.e., ≥3 food groups) with moderate portions	• Balanced meals tend to have balanced nutrient profiles • Helps prevent overeating high-potassium foods and beverages
2. Eat whole fruit and vegetables instead of juices	• Fruit and vegetable juices tend to be higher in potassium, lower in fiber, and more easily overeaten
3. Limit portions of potassium-dense foods (nuts, seeds, and dried fruit)	• Easy to consume too much potassium
4. Drain and rinse fluids from canned products	• Helps remove potassium • Also removes sodium and phosphorus
5. Avoid food products prepared with potassium-based food additives	• Additives can be a major source of potassium • Additive-free products are usually available
6. Use the nutrition facts panel to assess and compare products	• Helps to select lower potassium products • Percentage of DV based on a 3500-mg potassium diet (i.e., ≥6% DV (≥200 mg) = high potassium)
7. Demineralize and prepare foods using wet cooking methods	• Helps remove potassium • Also removes sodium and phosphorus • Must discard potassium-rich cooking water
8. Limit meals away from home	• Less control over food processing and preparation methods that may impact potassium content • Portion sizes tend to be larger than appropriate
9. Limit intake of high-potassium foods	• Reduce potassium intake

DV, Daily value.

When analyzing urine potassium output, urine creatinine should also be measured to assess completeness of urine collection, and normalize potassium output to a parameter that is tied to energy intake [27–30]. Daily urine creatinine excretion is expected to be approximately 18 mg/kg ideal body weight (IBW) in females and 23 mg/kg IBW in males [27]. Typical urine potassium-to-creatinine ratios (K/C) range from 37.5 to 62.5 mEq/g (1.5–2.5 mg/mg). Spot urine K/C has been proposed as a less demanding approach to assessing urine potassium output. However, urinary potassium excretion rates exhibit circadian rhythms and are highly dependent of the potassium content of the previous eating occasion [8,30]. In people with kidney disease, expected urinary creatinine excretion should be adjusted downward by 0.4 mg/kg per 1.0 mg/dL of serum creatinine above normal to account for extrarenal degradation [31]. Moreover, as diet-derived creatinine (primarily from meat) contributes up to 30% of urinary creatinine output, urine potassium-to-creatinine ratios may be exaggerated in patients who limit or avoid meat.

Another useful tool for evaluating urine potassium excretion is the transtubular potassium gradient (TTKG), which examines potassium concentrations in urine and blood in relation to the osmolality (TTKG = (urineK ÷ [serumK]) × (serumOsm ÷ urineOsm)), where K is potassium concentration and Osm is osmolality [32]. High TTKG values (>2) in hypokalemia suggest potassium wasting by the kidneys, whereas low TTKG values (<6) in hyperkalemia suggest impaired potassium secretion [32]. Importantly, TTKG assessment requires that urine sodium be >25 mEq/L, and urine osmolality exceeds serum osmolality [32].

Managing hyperkalemia

Prior to treating hyperkalemia, it is important to repeat the potassium blood test to rule out pseudohyperkalemias, which are frequent and can be caused by muscle contraction from fist clenching, or activation of platelets or lysis of blood cells from a tight tourniquet or delay in analyzing the blood sample. Very high levels of white cells, as seen in hematologic malignancies, can also lead to spurious high serum potassium concentrations, in a phenomenon called reverse pseudohyperkalemia [33].

If the serum potassium concentration is severely elevated, or if hyperkalemia is accompanied by clinical abnormalities, emergent treatment may be necessary. Clinical manifestations of hyperkalemia are related to severity and duration of the disturbance and typically involve muscle weakness, which can progress to flaccid paralysis, paresthesias, delayed deep tendon reflexes, and cardiac arrhythmias. Cardiac conduction changes associated with hyperkalemia can be assessed through an electrocardiogram (ECG) and progress from peaked T-waves, to PR prolongation, loss of P waves, QRS widening, bradycardia, and lastly a sine wave. Nonspecific ST changes can also occur. Emergent treatments for hyperkalemia typically include a combination of: (1) IV calcium to restore the transmembrane potential of contractile cells; (2) IV insulin and glucose to shift potassium intracellularly; and (3) dialysis to remove potassium.

Hyperkalemia in kidney disease is caused by excessive potassium intake, impaired potassium excretion, and/or reduced uptake and storage of potassium intracellularly. Even if the primary defect is unrelated to diet, nutrition interventions may help to address each of these problems. However, the dietary strategies are specific to the etiology and nonuniform and, therefore, should be tailored based on the nutrition assessment.

Lowering potassium intake

Lowering dietary potassium intake is considered to be a reasonable approach for managing hyperkalemia and can be achieved in several ways. One of the main strategies is to limit or avoid high-potassium foods (Table 21.5) [34]. However, although low-potassium diet plans have been in use for more than a half century, no studies have demonstrated their efficacy for treating hyperkalemia, and observational studies have failed to find a strong association between dietary potassium intake and serum potassium concentrations in hemodialysis patients [22]. This approach has many pitfalls and may exacerbate problems related to potassium excretion and distribution in the body, which could increase serum potassium concentrations [22,35].

As shown in Fig. 21.2, restricting high-potassium foods has the greatest potential to lower potassium intake while maintaining dietary balance within the fruit, vegetable, and protein food groups, where the potassium content is relatively high, and highly variable. Table 21.4 provides lists of low- and high-potassium foods for reference. Such lists can help to inform nutrition assessment and guide patient education. However, food lists should only be used in conjunction with medical nutrition therapy by a nutrition expert such as a registered dietitian.

One of the main flaws of the food list approach to dietary counseling is that food processing and preparation methods can add, concentrate, dilute, or remove potassium from foods, dramatically altering their potassium content (Fig. 21.3). In general, processes that add or concentrate potassium will increase the risk of hyperkalemia, and processes that dilute or remove potassium will decrease the risk of hyperkalemia.

Added potassium

Added potassium is primarily in the form of potassium salts in processed foods such as potassium

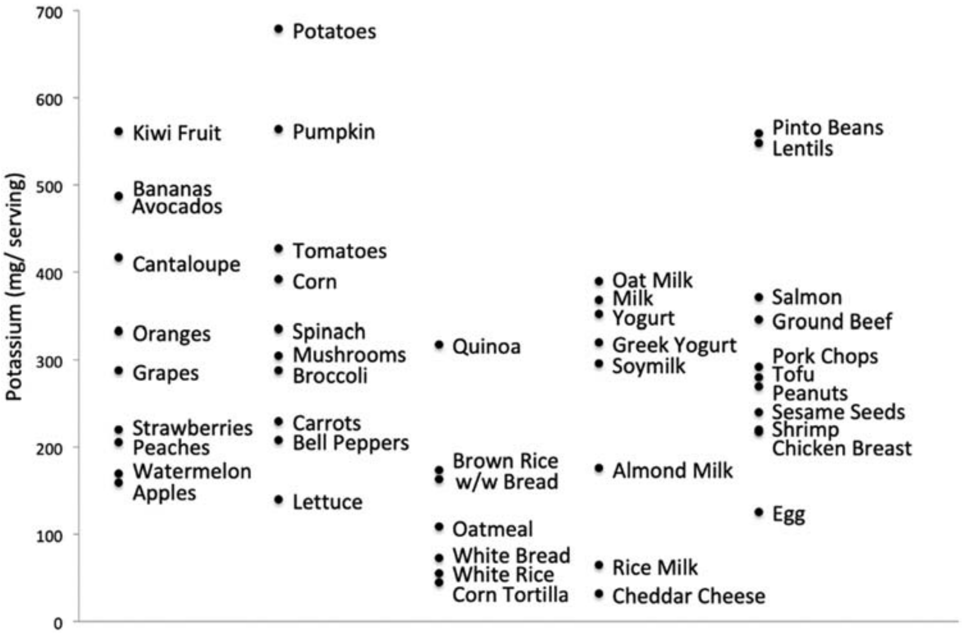

FIGURE 21.2 Potassium content of foods across food groups.

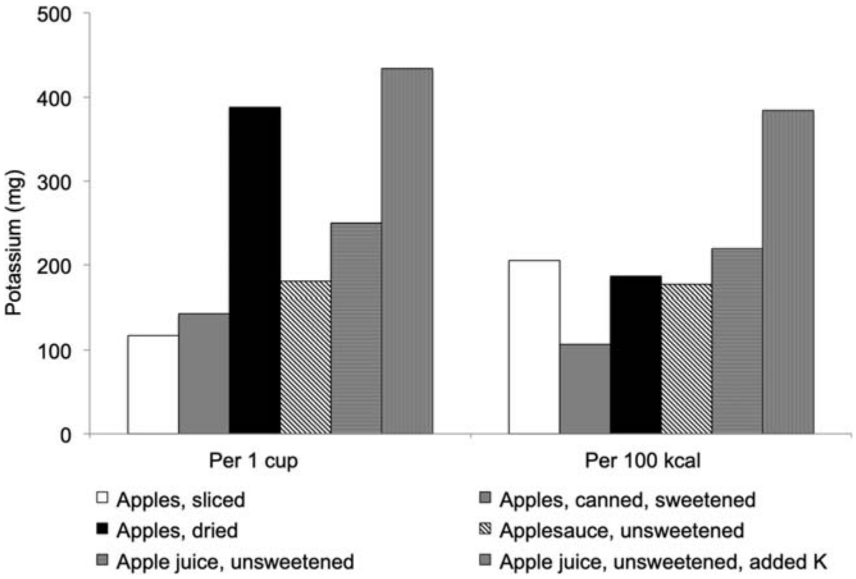

FIGURE 21.3 Effect of food processing and preparation of the potassium content of apple products.

chloride, potassium citrate, and potassium lactate. Although data on potassium additives is sparse, analyses of processed animal products suggest that the amount of added potassium is highly variable and can be substantial [36–38]. Indeed, animal products containing potassium additives have been found to contain approximately 150 mg more potassium per 100 g serving, reaching +600 mg potassium/serving for some products [36].

Potassium chloride deserves particular attention for people with kidney disease following a low-sodium diet because of its function as a substitute for table salt. Like sodium chloride (table salt), potassium chloride has a salty taste, making it widely used in low-sodium products. Potassium chloride–based salt substitute products are also available for use at home, and their use has been linked to several cases of hyperkalemia in people with kidney disease [39].

Potassium additives can usually be identified using the ingredients list, and additive-free alternatives are generally available. Most food products containing potassium-based food additives will contain a nutrition facts panel indicating the overall potassium content of the product. The amount of potassium on the nutrition facts panel is based on a 3500 mg potassium, 2000-cal diet. Foods containing ≥6% of the daily value for potassium (≥200 mg/serving) are typically considered to be high-potassium. However, serving sizes on food products can differ substantially from the portion consumed, and mislabeling of nutrients by manufacturers is relatively common [40]. Consequently, patients with hyperkalemia should be advised to avoid any processed foods prepared with potassium additives.

Concentrating and diluting potassium

Dehydrating and juicing can increase the amount of potassium in a standard portion of food. Because the amount of food consumed in a meal is primarily determined by its weight/volume, foods with high per portion potassium are more likely to contribute to postprandial hyperkalemia. For this reason, dried fruits are generally regarded as high-potassium foods, even if their hydrated counterparts are low in potassium (e.g., grapes and raisins) [34]. Similarly, juices tend to be consumed in amounts that exceed the usual intakes of their fruit and vegetable source, and excessive consumption of juice from even low-potassium fruit such as apple juice has been linked to hyperkalemic episodes [39]. Consequently, people with kidney disease should rarely consume dried fruit, and fruit and vegetable juices, and always in moderation.

In contrast to the amount of potassium in a meal, which depends on portion size, overall dietary potassium intake is primarily determined by potassium density, or the amount of potassium per calorie. Food processing and preparation can alter the potassium density of foods substantially by adding or removing energy-containing compounds. Factors that add calories such as adding sugars and frying foods in fat tend to reduce (dilute) the potassium density of foods, whereas factors that remove calories such as skimming and trimming fat tend to raise (concentrate) the potassium density of foods. For example, fat-free plain yogurt can contain as much as three times more potassium per calorie as sweetened high-fat alternatives. Importantly, adding empty calories to food reduces the intake of beneficial nutrients and may exacerbate other diet-related conditions (e.g., added sugar and hyperglycemia). As a result, this approach is not recommended for managing hyperkalemia.

Removing potassium

When foods are soaked and/or cooked with water, potassium diffuses from the food into the water, which can then be discarded (called "demineralization") [41]. The amount of potassium removed depends on the duration of soaking, temperature of the water, and surface area of the food. As a general rule, 30−60 minutes of soaking in hot water (100°F) is sufficient to cut the potassium content of foods in about half [41]. Demineralization has the added benefit of removing sodium and phosphorus from foods, but can also result in the loss of other heat-labile and water-soluble nutrients, and affects the palatability of certain foods [41]. Therefore people with kidney disease should primarily use demineralization on high-potassium foods that prepare well with wet cooking methods such as starchy vegetables, meat products, and legumes.

Increasing potassium excretion

The primary defects in potassium excretion in kidney disease occur at the kidney and are largely consequences of kidney disease pathogenesis or treatment that are not readily modified by diet. However, in advanced CKD, the GI tract becomes an increasingly important route of potassium excretion. Furthermore, constipation is relatively common [42], and stool outflow is the primary determinant of potassium excretion by the GI tract [20].

Fiber is the main dietary factor affecting stool output, and together with fluids and physical activity, are the chief lifestyle recommendations for preventing and treating constipation [43]. In healthy individuals, dietary fiber has been shown to increase potassium excretion in stool as much as threefold [5]. The majority of fiber in the diet comes from whole plant foods, including fruit, vegetables, whole grains, nuts, seed, and legumes, although fiber-based food additives and fiber supplements can also be major sources of fiber intake. As many dietary sources of fiber are also high in potassium, the benefits of increasing potassium excretion must be weighed against the potential for increasing potassium intake. However, patients with hyperkalemia, particularly those who report symptoms of constipation, should be encouraged to consume whole plant foods and engage in moderate intensity physical activity, as appropriate.

Increasing potassium uptake and storage in cells

Uptake of potassium into cells is critical for preventing postprandial hyperkalemia in people with kidney disease. As discussed previously, this process is mediated by the action of insulin on $Na^+–K^+$ pump activity. While this pathway is specific to potassium, macronutrients are needed to trigger insulin secretion. Consequently, patients with hyperkalemia should consume balanced meals, ideally prepared from scratch, as they are more likely to contain an appropriate balance of potassium and necessary macronutrients.

Postprandial potassium clearance is also highly dependent on usual potassium intake [15,16]. Although limiting potassium intake is recommended for managing hyperkalemia, strict adherence to a low-potassium diet reduces dietary potassium tolerance through adaptation, priming patients to postprandial hyperkalemia in the event that a high-potassium meal is consumed [15,16]. For this reason, patients following a low-potassium diet should be weary of processed food and meals consumed away from home, which may contain hidden sources of potassium (e.g., additives).

One of the main diet-related complications affecting the distribution of potassium in the body is metabolic acidosis [8]. Diet contributes up to half of the total acid load that is excreted by the kidneys in healthy individuals [44]. Dietary acid load is primarily generated from metabolism of basic and sulfur-containing amino acids into hydrochloric and sulfuric acid, respectively, and phosphate-containing salts (e.g., phosphoric acid) [44]. Acid in the body can be neutralized by base-forming organic acids, which are bound to minerals, especially potassium (e.g., potassium citrate), in fruits and vegetables [44]. Indeed, protein and potassium are key variables in equations for estimating dietary acid load [44]:

Net endogenous acid load $(\text{mEq/d}) = (54.5 \times \text{protein (g/d)}/\text{potassium (mEq/d)}) - 10.2$

Potential renal acid load $(\text{mEq/d}) = (0.49 \times \text{protein (g/d)}) + (0.037 \times \text{phosphorus (mg/d)}) - (0.021 \times \text{potassium (mg/d)}) - (0.026 \times \text{magnesium (mg/d)}) - (0.013 \times \text{calcium (mg/d)})$

An alkaline diet, low in acid-forming animal-based protein foods and high in base-forming fruits and vegetables, can be used to treat metabolic acidosis (total CO_2 <25 mEq/L) [45,46] and may have additional health benefits in people with kidney disease [46,47]. However, this approach has not been tested in patients with hyperkalemia and must be weighed against efforts to lower potassium intake [22].

Diabetes mellitus is another common cooccurring condition in people with kidney disease, which may contribute to hyperkalemia in several ways. For patients with β-cell failure requiring exogenous insulin or insulin-stimulating agents, balancing potassium intake with carbohydrates and medications is crucial for maintaining serum potassium and glucose homeostasis. As poor glycemic control can lead to conditions that increase serum potassium concentrations (e.g., hyporeninemic hypoaldosteronism, hyperglycemia, and ketoacidosis), dietary guidelines for managing diabetes mellitus should be followed in these patients.

Nondietary approaches to hyperkalemia

Nondietary strategies may be equally or more effective in managing hyperkalemia and should be explored:

1. May be possible to address iatrogenic causes by adjusting dialysis and medications regimens (Table 21.3, Fig. 21.1).
    a. Medications for RAAS inhibition.
    b. β-Blockers, heparin, and NSAIDS.
2. May be able to address underlining etiology.
    a. Treat AKI, if possible, which should return potassium to normal.
    b. Metabolic acidosis and constipation may be treated with medications.
3. May be able to provide treatments to increase potassium excretion.
    a. Increase dialysis or improve adherence.
    b. Potassium binders (discussed further next).
    c. Carbonic anhydrase inhibitors, loop diuretics, and thiazide diuretics can all contribute to kaliuresis. In patients with eGFR of less than 30 mL/min/1.73 m^2, loop diuretics are the preferred agent.

Currently, potassium binders are used both in acute and chronic hyperkalemia management. In acute hyperkalemia, binders are used in conjunction with emergent treatment strategies for hyperkalemia. In chronic hyperkalemia, binders are also used to maintain normokalemia from underlying disease, and increasingly to continue medications that can cause hyperkalemia, but have other beneficial effects (usually RAAS inhibitors) [48].

In 1958 the FDA approved the first potassium binder for the treatment of hyperkalemia. Sodium polystyrene sulfonate (SPS) (brand name Kayexalate) is an exchange resin where sodium and hydrogen ions are exchanged for other cations in the colon [49]. It is available as a powder, and in a mixture with sorbitol (20 g of sorbitol per 15 g of SPS). There are also 1500 mg of sodium per 15 g dose. The exchange function of this medication is not specific to potassium. Magnesium and calcium can also be bound. Each 1 g of SPS is thought to bind 1 mEq of potassium [50]. For decades, this was the only oral exchange resin available and widely used for hyperkalemia. Its use has been called into question, as at the time it was approved, the FDA did not require a demonstration of efficacy for approval, and safety concerns over bowel necrosis and other reported GI side effects [51]. In 2009 the FDA used a warning to regarding these side effects and to avoid concomitant administration of sorbitol [49]. Despite this the combination is still widely available. The large stool volume from the sorbitol is thought to be a mechanism for its potassium lowering [52,53]. Two randomized clinical trials using SPS have been complete. In one trial of CKD patients the mean potassium concentration decreased for 5.8 ± 0.6–4.3 ± 0.5 mEq/L by day 3 with 5 g thrice daily dosing. Magnesium levels were not measured [51]. In the other study of 33 CKD patients, SPS did normalize serum potassium levels in 73% of the patients taking it for 7 days. Hypomagnesemia was observed in 31.3% of patients, and hypocalcaemia in 18.8% of treated patients [54]. Retrospective data have shown that a single 30-g dose decreases serum potassium by a median of 0.8 mEq/L in CKD stages 4 and 5 [55]. These small studies did demonstrate efficacy, but the variable time to normokalemia, and other reports of adverse events, do challenge its places as standard therapy for acute and chronic hyperkalemia. The concerns over sodium load and GI toxicity continue to limit the use of this drug.

Patiromer (brand name Veltassa) was the next nonabsorbed binder approved. It exchanges calcium for potassium or other cations in the colon, where potassium concentrations in the gut are highest [56]. The use of calcium rather than sodium to exchange for potassium ameliorates the risk of sodium loading seen with other potassium binders [56]. Patiromer was well tolerated in clinical trials of CKD patients on RAAS blockers [57]. In the Amethyst-DT clinical trial of CKD patients with diabetic kidney disease, the range of potassium decrease was dose-dependent and ranged from a mean reduction of 0.35 to 0.97 mEq/L, depending on the dose. Constipation and hypomagnesemia requiring repletion are common reported side effects [57], although increases in urinary calcium excretion, and decreases in urinary phosphorus and sodium excretion have also been noted. Patiromer also appeared to be generally well tolerated in heart failure patients in that trial [58].

Sodium zirconium cyclosilicate (brand name Lokelma) is a nonabsorbed compound that binds preferentially exchanges hydrogen and sodium for potassium and ammonium in the gut. The compound is highly selective for potassium compared to magnesium [59]. Binding can occur throughout the gut, making it attractive for consideration as both an acute and chronic therapy [60]. Each 5-g dose (the lowest dose) of Lokelma contains about 400 mg of sodium, and the recommended doses range from 5 g daily to 10 g thrice daily depending on the clinical scenario. In one clinical trial, potassium lowering occurred in a dose-dependent fashion up to an average of 0.7 mEq/L in the 10 g thrice daily dose at 48 hours [61]. Edema has been reported in patients receiving higher doses [62].

Managing hypokalemia

Although decline in glomerular filtration from loss of functional nephrons promotes hyperkalemia, kidney disease is also associated with hypokalemia, which can be just as dangerous. Similar to hyperkalemia, consequences of hypokalemia are principally caused by disturbed action potentials in neurons and muscle cells. Symptoms and signs of hypokalemia usually manifest once serum potassium fall below 3.0 mEq/L and include muscle cramping, weakness and/or paralysis, constipation, and torsades de pointe [63]. Severe hypokalemia can result in rhabdomyolysis and heart failure, and if prolonged, can exacerbate kidney disease, as seen in interstitial nephritis and nephrogenic diabetes insipidus [63]. ECG changes seem with hypokalemia include U-waves, T-wave flattening, and ST segment changes [63].

Treatment for hypokalemia is directed toward repleting potassium stores, if necessary, and if possible, addressing the underlying cause(s) of hypokalemia. Potassium repletion is usually achieved with oral potassium chloride (KCl; brand name Slow-K). However, if hypokalemia is severe (<2.5 mEq/L), or if it associated with a GI conditions that preclude oral repletion, or clinical symptoms and signs of hypokalemia, KCl should be provided intravenously with great caution regarding vascular access and flow rate. To prevent side effects and rebound hyperkalemia, potassium repletion should not exceed 20 mEq of KCl (approximately 800 mg) of potassium at one time. In addition, before attempting to replete potassium, it is important to assess for and address concurrent hypomagnesemia, which occurs in nearly half of cases and can lead to potassium-refractory hypokalemia [64].

Hypokalemia in kidney disease is caused by inadequate potassium intake, excessive potassium losses, and/or increased uptake and storage of potassium intracellularly (Fig. 21.1). Because potassium is ubiquitous in the diet (Fig. 21.2), inadequate potassium intake is rarely caused by consuming a low-potassium diet but may occur secondary to malnutrition. To avoid refeeding syndrome, malnourished patients should increase energy intake slowly (200–300 kcal/day), and closely monitor electrolytes for abnormalities. Normal serum potassium concentrations are not required before treating malnutrition. However, increasing energy intake will trigger insulin-mediated potassium uptake by cells, so patients with hypokalemia should receive prophylactic potassium when treated for malnutrition.

Potassium losses in people with kidney disease can occur via multiple routes, primarily the kidneys, dialysis, and GI tract. Excessive potassium losses causing hypokalemia often requires supplemental potassium to replete body stores and changes to medication and dialysis to treat. Although diet is unlikely to be the primary cause of vomiting and diarrhea in people with kidney disease, it may have a role in managing these conditions. Importantly, as vomiting and diarrhea are broad, nonspecific symptoms with varied pathophysiologies, dietary intervention should be tailored based on the patient's response to food.

Patients with chronic vomiting should try limiting potentially nauseating or offending foods (e.g., foods with strong odors), and consuming small/frequent, bland meals [65]. In kidney disease, nausea and vomiting may be caused by uremia, particularly as blood urea nitrogen levels rise above 160 mg/dL. Such patients may benefit from limiting protein intake [35,66]. Another potential cause of vomiting in this population is gastroparesis [65]. In these patients, limiting dietary fat and fiber intake and consuming liquid nutrition sources can speed gastric emptying. However, these modifications are likely to increase dietary glycemic index, which could actually worsen gastroparesis in people with diabetes, if glycemia is not controlled.

Patients with chronic diarrhea should try limiting foods containing nutrients that tend to be poorly absorbed, osmotically active, and/or highly fermented in the GI tract. Some notable examples include fats, soluble fibers, lactose, and fructose. The low-FODMAP diet (Fermentable, Oligo-, Di-, Mono-saccharides And Polyols) has been shown to reduce diarrhea symptoms in patients with irritable bowel syndrome and may be beneficial in some patients. If diarrhea is severe and intractable, a nil per os or empirical elimination diet may be trialed temporarily to help identify dietary culprits. Hidden drugs consumption such as diuretics and laxatives should also be searched for, as they can lead to long-term hypokalemic status and secondary tubulointerstitial disease and kidney failure.

Case study—hyperkalemia in chronic kidney disease

Referral: New-onset hyperkalemia

History of present illness: 61-year-old diabetic male with no acute complaints. Mr. S reports complete adherence to prescribed medications, which have not changed since previous visit with normal serum potassium concentration (4.8 mEq/L). He was referred by his doctor for hyperkalemia on two subsequent laboratory tests. He reports that he has not self-monitored his blood sugars for many years.

Review of systems is negative except for occasional constipation. He has two bowel movements per week with difficulty.

Past medical history: Stage G4A3 CKD (12 years), T2D (18 years), HTN (18 years)

Medications/supplements: Ramipril (5 mg), Losartan (25 mg), insulin withheld for fasting blood tests.

Sociodemographics: non-Hispanic white male, lives with spouse, employed full-time (attorney), income meets needs.

Physical exam findings: Wt: 85 kg, Ht: 5′7″, BMI: 29.4 kg/m^2, WC: 42″, BP: 131/83 mmHg, HR: 84 bpm. Mr. S weight has been stable. His BMI is classified as overweight (29.4 kg/m^2), and his waist circumference was 42″, indicating central adiposity.

General: well appearing, well-nourished male

Heart: normal rhythm

Lungs: no crackles/rales

Extremities: 1+ bilateral pitting edema

Diet history: Dietary recall indicates that Mr. S was fasted during blood testing, except for his usual mug of plain, black coffee. His most recent eating occasion was a bowl of low-sodium microwave popcorn, which he consumes most evenings while watching TV. Mr. S reports that he has been trying to incorporate more kidney-friendly foods since his checkup in July. In particular, he has replaced his usual cola with cranberry juice and started eating cauliflower with ranch dressing as a snack. Three-day food records indicate that Mr. S consumes a typical Western diet, high in grains and animal-based protein foods, and low in fruit, vegetables, and dairy products. Approximately half of his meals are consumed away from home and homemade meals (prepared by Mr. S) tend to be processed or ultraprocessed rather than unprocessed or minimally processed. His juice consumption is around three cups per day (contain 250–750 mg potassium/cup) and makes up the majority of his fruit and vegetable intake.

Laboratory report:

	10.18.19	10.20.19	10.21.19	Reference
Blood				
RBC	4.7			4.7–6.1 mil. cells/μL
Hgb	**12.7 L**			13.5–17.5 g/dL
Hct	**42 L**			45%–52%
WBC	8111			40,000–11,000 cells/μL
Platelets	230,000			150,000–450,000 cells/μL
Na^+	141			135–145 mEq/L
Cl^-	105			96–106 mEq/L
BUN	**80 H**			7–20 mg/dL
Glucose	**107 H**			70–100 mg/dL
K^+	**5.9 H**	**6.1 H**		3.5–5.0 mEq/L
HCO_3^-	23			23–29 mEq/L
Cr	**4.2 H**			0.6–1.2 mg/dL
PO_4^-	**5.3 H**			2.5–4.5 mg/dL
Total Ca^{+2}	9.3			8.5–10.5 mg/dL
Albumin	4.1			3.4–5.4 g/dL
eGFR	**16 L**			> 120 mL/min/1.73 m^2
HbA1c	**8.1 H**			4.0%–5.6%
Osmol	**298 H**			275–295 mmol/kg
Urine				
K^+			31	25–125 mEq
UUN			17.3	12–20 g
Cr			1612	955–2936 mg
Osmol			756	500–800 mmol/kg
Volume			**510 L**	800–2000 mL
MACR	500		400	0–30 mcg/mg

Questions:

1. Is potassium excretion impaired?

   Yes, urinary potassium output is low in relation to reported intake, as well as creatinine and urea nitrogen excretion. The TTKG is also low (3.9). This may be caused by RAAS inhibitors and/or hyporeninemic hypoaldosteronism secondary to uncontrolled diabetes mellitus. Stool potassium output was not measured but may be limited by constipation.
2. What short-term factors may have contributed to hyperkalemia?
   a. Coffee is a relatively high-potassium beverage and is low in insulin-stimulating nutrients.
   b. Exogenous insulin was withheld during fasting blood tests to prevent hypoglycemia, but prolonged fasting and hypoinsulinemia can contribute to hyperkalemia.
3. How should potassium intake be evaluated and monitored in this patient?
   a. 3-day food record with targeted diet history based on intervention.
   b. 24-hour urinary potassium and creatinine.
4. What pharmacologic interventions are available for the management of this patient?

   - **a.** Diuretics can increase kaliuresis.
   - **b.** Addition of alkalinizing agent to promote kaliuresis, and intracellular shift of potassium.
   - **c.** Stop dual RAAS inhibition, which is known to be associated with an increased risk of hyperkalemia.
   - **d.** Laxatives to treat his constipation.
   - **e.** Potassium-binding agents may be considered if other changes are inadequate, or current RAAS inhibiting medications cannot be decreased.

5. What diet-related problems may be contributing to hyperkalemia in Mr. S, and why?
   - **a.** Consuming meals away from home. Unable to control and difficult to assess food processing and preparation factors that may increase potassium intake (e.g., additives). Meals and portion sizes are often unbalanced.
   - **b.** Excessive consumption of potassium-rich beverages, which are concentrated sources of potassium; some without adequate amounts of insulin-stimulating macronutrients (e.g., black coffee). Lack dietary fiber.
   - **c.** Low-dietary fiber intake. May contribute to infrequent bowel movements, reducing potassium excretion in stool.
   - **d.** Intake of high-potassium foods (e.g., fruit juice).
   - **e.** Excessive dietary acid load. May contribute to metabolic acidosis, reducing potassium uptake by cells.

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CHAPTER

22

Magnesium and kidney disease

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Introduction

Magnesium (Mg) is the fourth most abundant cation in the body and the second most important intracellular cation [1]. It is an essential cation for multiple processes in the body playing an important role in neuromuscular processes, as a cofactor in multiple enzymatic reactions, in mineral bone metabolism, adenosine triphosphate metabolism, neurotransmitter release, and in the regulation of vascular tone, heart rhythm, and platelet-activated thrombosis [2,3].

Chronic kidney disease (CKD) affects approximately 13% of the general population [4] and is associated with the increased risk of cardiovascular disease (CVD) because of both traditional and nontraditional CVD risk factors [5]. Epidemiological studies have found positive correlations between higher levels of Mg and improved survival among patients suffering from CKD and end-stage renal disease (ESRD) [6,7], while hypomagnesemia is significantly associated with cardiovascular and all-cause mortality in patients with CKD and ESRD [8]. However, data are sparse regarding evidence-providing, prospective, randomized, controlled trials investigating the impact of Mg supplementation upon the reduction of these cardiovascular risks and improved CV outcome [9].

Serum magnesium in chronic kidney disease

Magnesium is predominantly an intracellular cation, approximately one-third of the total Mg in the body being present in the intracellular space, a small amount (2%) in the extracellular space, the remainder (56%) in bone [3]. Less than 1% of the total body Mg is present in the intravascular compartment [10]. Normal serum Mg concentrations range from 0.7 to 1.1 mmol/L (1.4–2.0 mEq/L or 1.7–2.4 mg/dL) and can be categorized into three fractions: ionized (55%–70%), protein-bound (20%–30%), and complexed with anions such as phosphate, bicarbonate, citrate, or sulfate (5%–15%).

As with other electrolytes, Mg homeostasis depends on the balance between gastrointestinal absorption and kidney excretion and changes in intake being balanced by changes in renal Mg reabsorption, principally in the loop of Henle and the distal tubule. The kidney provides the most sensitive control for Mg balance and although the renal handling of Mg is highly adaptable, this ability deteriorates when renal function declines significantly.

The average daily Mg intake is 360 mg (15 mmol), approximately one-third being absorbed, principally in the small bowel through both an active and passive diffusion. The renal handling of Mg depends mainly on its plasma concentration, calcium levels (hypercalcemia inhibits Mg reabsorption), and several other factors like metabolic alkalosis that stimulates reabsorption in contrast with metabolic acidosis, hypokalemia, and phosphate depletion which inhibit Mg reabsorption. Diuretics also affect Mg handling, thiazide diuretics being associated with Mg wasting, and amiloride with distal tubular reabsorption of Mg.

Contrary to other ions that are maintained within a narrow range by the action of several hormones, Mg is treated differently: there are no hormones that have a substantial role in regulating urinary Mg excretion, and bone, the principal reservoir of Mg, does not readily exchange with circulating Mg. Thus in the setting of negative Mg balance, the plasma Mg concentration falls rapidly with negative Mg balance, leading to a

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marked reduction in Mg excretion. Conversely, there is no protection against hypermagnesemia with the loss of renal function. In this setting, continued intake leads to Mg retention that is predominant in the extracellular fluid.

Modulation of serum magnesium in chronic kidney disease patients

Magnesium dosing

In moderate CKD the increase in the fractional excretion of Mg largely compensates for the loss of glomerular filtration rate (GFR) to maintain normal serum Mg levels. However, in more advanced CKD [as estimated GFR (eGFR) falls <30 mL/min], this compensatory mechanism becomes inadequate such that overt hypermagnesemia might occur in patients with eGFR < 10 mL/min. However, observational data do not support this hypothesis, in the real life, both CKD and ESRD patients have normal serum levels of Mg and sometimes even low serum Mg concentration [11]. This is due to the intake of Mg coupled with other dietary intake which might interfere with intestinal absorption and dialysate Mg concentration or some drugs such as thiazide diuretics, proton-pump inhibitors (PPIs), cisplatin, aminoglycoside antibiotics, and calcineurin inhibitors. Moreover, recent evidence highlights the role of proteinuria in inducing renal Mg wasting tubular injuries, which explains the high prevalence of HypoMg in CKD [12].

Alterations in circulating serum Mg concentrations are offset by intracellular stores, so that a negative daily Mg balance may not manifest with lower Mg concentrations. Intracellular Mg depletion and normal serum Mg concentrations may coexist, and total Mg deficiency might not manifest until cellular stores are exhausted. Therefore using serum Mg levels to diagnose Mg deficiency may not be very accurate.

Since 99% of Mg is intracellular, Mg concentrations in body tissues or blood cells (i.e., erythrocytes) were thought to be a better marker for Mg deficit or overload. Erythrocyte Mg concentration was found to be higher in CKD patients than healthy volunteers, although an inverse correlation between Mg concentration of erythrocytes and hematocrit was found, suggesting that anemia, rather than renal failure, might explain the high concentration of Mg in erythrocytes [13,14].

Drugs associated with hypo or hypermagnesemia

Certain drugs widely used in patients with CKD can decrease gastrointestinal ingestion or kidney excretion of Mg and potentially cause hypomagnesemia, while other Mg-containing drugs (e.g., certain laxatives and antacids) may induce hypermagnesemia, particularly in those with impaired renal function [15] (see Table 22.1).

PPIs are potent blockers of gastric acid secretion, used by millions of patients suffering from gastric acid–related complaints; although in general they have a good safety profile, their long-term use is associated with decreasing the Mg intestinal absorption via an unknown mechanism. This might be related to the decreased function of TRPM 6/7 channels, the site of active intestinal Mg transport [16]. This channel is particularly important in times of low Mg intake and might explain why malnutrition is a specific risk factor for PPIs-associated hypomagnesemia.

Cation exchange polymer has been long time used as a treatment for hyperkalemia, particularly in those with CKD. Hypomagnesemia does not typically occur with sodium polystyrene sulfonate exposure, but newer

TABLE 22.1 Drugs interference with serum Mg level.

Drugs associated with hypoMg	Drug associated with hyperMg
Proton-pump inhibitors	Laxatives (Mg hydroxide or Mg sulfate) and enemas
Cation exchange polymer (stool softeners–docusate, stimulants—senna, osmotic laxatives, and patiromer)	Mg-containing phosphate binders
Loop and thiazide diuretics	SGLT2 inhibitors—canagliflozin, empagliflozin, and dapagliflozin
Antimicrobials (including antifungals and antivirals)—aminoglycosides, amphotericin B, and foscarnet	
Calcimimetics	
Immunosuppressives—cyclosporine, tacrolimus	
Chemotherapy—cisplatin, carboplatin, monoclonal antibodies blocking the epidermal growth factor receptor like cetuximab and panitumumab	

SGLT-2, Sodium–glucose cotransporter 2.

agent, patiromer, was associated with significantly more cases of hypomagnesemia than placebo in a recent multicenter randomized controlled trial in CKD patients [17].

Loop and thiazide diuretics inhibit Mg reabsorption in the loop of Henle and distal convoluted tubules (DCT), respectively. However, the effect of loop diuretics on Mg concentrations is generally mild. In the clinical setting of diuretic-induced hypomagnesemia, when continued diuretic use is warranted, the addition of potassium sparing diuretics such as amiloride might be useful. These drugs may decrease Mg wasting by increasing reabsorption in the distal nephron [18].

Many other drugs like *antimicrobials*, *calcimimetics*, *immunosuppressives*, or *chemotherapy* may induce hypomagnesemia via a direct tubular toxic effect or decreased expression of TRPM6 in the DCT, respectively.

Conversely, others drugs like *laxatives, enemas, phosphate binders, or even sodium–glucose cotransporter 2 (SGLT-2) inhibitors* are associated with hypermagnesemia in the setting of impaired renal function. Magnesium, by increasing the intestinal osmotic gradient and consequent water movement, is an important component of many laxatives and enemas; the risk of hypermagnesemia is directly proportional to the amount of Mg ingestion and the kidney excretory capacity. This may become clinically relevant especially in setting of advanced CKD (stages 4 and 5), Mg-free containing preparation are preferred.

Magnesium-containing phosphate binders might induce hypermagnesemia, but this is generally well tolerated without any toxic effect [19]. Sevelamer hydrochloride, a calcium-free intestinally nonabsorbed polymer, is also associated with hypermagnesemia through its capacity of binding biliary salts thereby increasing free Mg for intestinal absorption [20].

SGLT-2 inhibitors are a new class of antidiabetic medications indicated for treatment for type 2 diabetes mellitus because they inhibit glucose reabsorption in the proximal tubule, thereby increasing urinary glucose excretion and reducing plasma glucose concentrations. A large body of new evidence underlines a positive effect for these agents in decreasing the cardiovascular risk and even the risk of CKD progression [21]. SGLT2 inhibitors have been associated with increasing serum Mg, through an improved insulin sensitivity, increase in plasma glucagon leading to increase in Mg reabsorption at the DCT, osmotic diuresis from glycosuria leading to electrolyte abnormalities, and/or SGLT2 inhibitor effect on TRPM6/TRPM7 channels in the DCT. The incidence of hypermagnesemia has not been well defined in studies because severe CKD patients were excluded from these studies. Currently, the use of SGLT2 inhibitors is restricted to patients with eGFR > 45 mL/min/1.73 m^2.

Magnesium and outcomes

Magnesium and vascular calcification in chronic kidney disease patients

CVD is the leading cause of death in the CKD population, the high prevalence of vascular calcification (VC) having a significant role to this cardiovascular risk [22]. The pathogenesis of VCs in CKD patients is complex, but it appears that Mg plays an important role in preventing VC in these patients. These positive effects are thought to be mediated by an antagonistic effect of Mg on the procalcifying milieu in CKD [10]. Thus in vitro data suggest that adding or increasing Mg may prevent calcification induced by calcium and high phosphate by the upregulation of factors that inhibit calcification and the downregulation of factors that promote calcification [23,24]. Furthermore, in other model of experimental uremia, Mg supplementation alone reduces ectopic calcification severity [25]. These experimental data were also confirmed in humans in small clinical trial of Mg supplementation in predialysis and ESRD patients [26]. Although it is well known that the uremic toxin indoxyl sulfate aggravates VC, administration of the oral carbon adsorbent AST-120 did not influenced the progression of VC, while supplementation with Mg did so [25]. Therefore Mg supplementation could potentially be a therapeutic option to attenuate the progression of VC in CKD. Because serum Mg depends on its renal excretion, Mg therapy might be associated with hypermagnesemia in CKD patients. This hypothesis was not confirmed by a small recent randomized controlled trial in which oral Mg supplementation in subjects with CKD stages 3 and 4 was safe and well tolerated. Although both serum and urine Mg increased, this was not associated with increased intracellular Mg or significant serious adverse events related to the study medication [27].

A deficiency in Mg promotes hydroxyapatite formation and calcification of vascular smooth muscle cells [28]. On the other hand, chronic hypermagnesemia in dialysis patients plays an important role in the genesis of adynamic bone disease, although the exact mechanisms are not yet clear [29,30]. Additionally, Mg prevents the maturation of calciprotein particles and, thus, VC progression—transformation from soluble nanoparticles containing amorphous calcium phosphate into elongated particles containing crystalline hydroxyapatite.

Magnesium and mortality in chronic kidney disease

In recent years, many observational studies have shown that Mg concentrations are positively associated with better survival in CKD cohorts and more importantly, this association seems to be robust and remained after adjusting for multiple covariables, including comorbidity and surrogates of nutritional status (body mass index, albumin) [6,31,32].

Several potential mechanisms explaining the role of Mg in clinical outcomes in CKD patient were postulated. First, lower serum Mg concentration has been associated with increased risk for sudden death in CKD patients mainly related to cardiac dysrhythmia [31]. Hypomagnesemia is associated with electrographic disturbances, including tachyarrhythmia and prolonged duration of repolarization, because it is well known that Mg in involved in the molecular mechanisms of cardiac excitation [33]. Mg has a role in establishing, and the maintenance of, the resting transmembrane potential being a critical cofactor for the Na/K-ATPase. Thus hypomagnesemia leads to a decreased activity of Na/K-ATPase which lowers the intracellular potassium concentration promoting hyperexcitability through a low resting membrane potential more close to the threshold potential. Mg also regulates the function of multiple other ion channels (notably sodium and calcium channels) during the course of the action potential as well. As a consequence, Mg depletion may prolong the depolarization time and make the heart more vulnerable to arrhythmia.

Moreover, in patients with CKD, a lower serum Mg is associated with a higher left ventricular mass index, thus providing another possible causal explanation of the association between serum Mg and cardiovascular mortality in CKD patients [34].

And finally, Mg also affects blood pressure and endothelial function. Higher serum Mg concentration is associated with improved endothelial dysfunction in patients with CKD, demonstrated by increased flow-mediated dilation, and in the general population serum magnesium is inversely associated with incident hypertension [6,35]. Despite the accumulating literature data suggesting the association between higher Mg level and a more favorable outcome, the effect of Mg administration on mortality in CKD patients has never been investigated as a primary end point. Therefore randomized, controlled trials designed to address the role of Mg in survival are required to preclude stronger conclusion.

Nutritional aspects

Daily requirement for Mg in adults is estimated to be 8–16 mmol (200–400 mg), values close to the recommended daily allowance (420 mg/day for adult males and 320 mg/day for adult females) [36]. While Mg is widely distributed in most human foods, it is important to note that only 30% of ingested Mg is absorbed across the intestine, utilizing both paracellular and active transport mechanisms. While 35% of absorbed Mg complexes to either albumin or other anions, the remaining circulates unbound, fluxing between the serum and the much larger intracellular depot. It is also important to note that phytic acid, the storage form of phosphorus in seeds, nuts, beans, legumes, and grains, can bind to Mg in the gastrointestinal tract, making it less available to our bodies.

Regarding the Mg content in the diet, it is widely found in green leafy vegetables (Mg is in the center of the chloride ring of chlorophyll molecules), beans, legumes, and nuts, while processed foods are poor in this cation (see Table 22.2). In CKD and especially ESRD patients, the current dietary prescriptions that limit the intake of potassium may also lead to a low Mg intake. In contrast a vegetarian diet meets the daily nutrient requirement for Hemodialysis patients according to National Kidney Foundation guidelines [37].

Growing evidence supports the health benefits of plant-based diets, such as the *Dietary Approaches to Stop Hypertension* diet, which are high in Mg, fiber and low in saturated fat and have low levels of sodium for preventing heart disease and hypertension [54]. Contrary to traditional dietary recommendations that limit the intake of fruits and vegetables because of their high potassium content in patients with CKD, these patients should be encouraged to consume more plant-based proteins since it is well known that meat-based diets are typically much more acidic than plant-based diets, and there are health benefits associated with changing the acid–base balance in the diet.

Another concern among nephrologists is related to the possible risk of malnutrition associated with a vegetable-based diet since they are considered nutritionally inadequate, being deficient in all the essential amino acids and, therefore, dangerous for the management of patients with CKD. However, these vegetable-based diets are sufficient for a balanced protein intake [55]. In fact, the European Prospective Investigation into Cancer and Nutrition-Oxford support the idea that well-balanced and diverse vegetable-based diets can be nutritionally adequate and beneficial [56].

Conclusion

Nephrologists should increase their awareness regarding the role of Mg in their patients since higher Mg serum levels might be associated with more favorable outcomes. Possible mechanisms underlying this association include protective effects of higher magnesium concentrations on the development of arrhythmia, ventricular hypertrophy, media VC, hypertension, and endothelial dysfunction. A low intake of fruits and

TABLE 22.2 Diet sources of Mg.

	Content of Mg	Potential benefits/particularities
Whole grain (wheat, oats and barley, as well as pseudocereals like buckwheat and quinoa)	A 1-ounce (28-g) serving of dry buckwheat contains 65 mg of Mg	– Many whole grains are also high in B vitamins, selenium, manganese, and fiber. – They reduce inflammation and decrease CV risk – Pseudo cereals like buckwheat and quinoa are higher in protein and antioxidants than traditional grains like corn and wheat; they also are gluten free so may be advise to patients with celiac disease [38,39]
Seeds (including flax, pumpkin, and chia seeds)	Pumpkin seeds—150 mg of Mg in a 1-ounce (28-g) serving	– Seeds are rich in iron, monounsaturated fat, omega-3 fatty acids, and extremely high in fiber – Antioxidant effect [40]
Dark chocolate (at least 70% cocoa)	64 mg of Mg in a 1-ounce (24 g) serving	– It is also high in iron, copper, and contains prebiotic fiber [41] – It contains flavanols that are powerful antioxidant [42]
Avocados	One medium avocado provides 58 mg of Mg	– It is also high in potassium, B vitamins, and vitamin K and unlike most fruits monounsaturated fat – They are an excellent source of fiber – Eating avocados can reduce inflammation, improve cholesterol levels, and increase feelings of fullness after meals [43–45]
Nuts (almonds, cashews, and nuts)	1-ounce (28-g) serving of cashews contains 82 mg of Mg	– A good source of fiber and monounsaturated fat and have been shown to improve glycemic control and dyslipidemia [46] – Nuts also have antiinflammatory effects and reduce appetite when eaten as snacks [46,47]
Legumes (lentils, beans, chickpeas, peas, and soybeans)	1-cup serving of cooked black beans contains an impressive 120 mg of Mg	– Legumes are also high in potassium and iron and a major source of protein for vegetarians [48] – They are rich in fiber and have a low glycemic index [49,50]
Tofu	3.5-ounce (100-g) serving has 53 mg of Mg	– Has high-protein content-one serving provides 10 g of protein and 10% or more of the RDI for calcium, iron, manganese, and selenium – Potentially protects against gastric cancer [51]
Fatty fishes	Half a fillet (178 g) of salmon packs 53 mg of Mg	– The fish meat is rich in potassium, selenium, and B vitamins – A high intake of fatty fish has been linked to a decreased CV risk [52]
Leafy greens (kale, spinach, collard greens, turnip greens, and mustard greens)	a 1-cup serving of cooked spinach has 157 mg of Mg	– They are a source of several nutrients, including iron, manganese, and vitamins A, C, and K. – Reduce cancer risk [53]

CV, Cardiovascular; *RDI*, recommended daily intake.

vegetables, the used of processed foods, low dialysate magnesium concentrations, or concurrent use of PPIs may put patients with CKD at risk for absolute or relative magnesium deficiency with detrimental effect for their outcome. Although Mg supplementation might represent an attractive option to these patients, this has to be confirmed in the future by higher evidence data.

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CHAPTER

23

Calcium, phosphate, PTH, vitamin D, and FGF-23 in CKD-mineral and bone disorder

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In healthy individuals, kidneys play an important role in regulating calcium and phosphorus homeostasis through different mechanisms. Chronic kidney disease (CKD) is associated with the inability to control normal mineral homeostasis, resulting in changes in serum levels of calcium, phosphorus, parathyroid hormone (PTH), vitamin D, and fibroblastic growth factor (FGF-23). Secondary hyperparathyroidism (SHPT) is present in early stages of CKD, leading to the development of high bone turnover, pathological fractures, vascular calcifications, and other systemic manifestations. The term "CKD-mineral and bone disorder (CKD-MBD)" was introduced to define the biochemical abnormalities of calcium, phosphorus, PTH, vitamin D metabolism, abnormalities in bone turnover, volume and bone mineralization, and vascular or other soft-tissue calcifications [1,2]. This chapter will review the calcium, phosphorus, PTH, vitamin D, and FGF-23 axis, with the main focus on phosphorus and its central role in the pathophysiology and progression of CKD-MBD.

Calcium metabolism

Calcium plays an important role in bone mineralization as well as a wide range of biological processes. Total body calcium content in adults is approximately 1000 g. Precisely 99% of total body calcium is in skeleton in the form of hydroxyapatite. The remainder is contained in the extracellular fluid and soft tissues. Serum and extracellular calcium concentration in humans is tightly controlled within a narrow physiologic range that is optimal for proper cellular functions of many tissues. Approximately 50% of the total serum calcium is ionized, and the remainder is bound primarily to albumin (about 40%) or complexed with anions such as phosphate and citrate (about 10%). Serum calcium levels range between 8.5 and 10.5 mg/dL (2.1−2.6 mM) in healthy individuals. The ionized fraction of calcium is physiologically important and is regulated by the calcium-regulating hormones, PTH, and 1,25-dihydroxyvitamin D.

The average calcium dietary intake is around 1000 mg/day, but there are wide variations. On average, 400 mg of calcium undergoes net absorption from the diet, and the unabsorbed and secreted components appear in the stool. Yet from the extracellular pool of calcium, which contains about 900 mg, 10,000 mg/day is filtered at the glomerulus, most being reabsorbed by the renal tubules, and only a few hundred milligrams appearing in urine each day. This extracellular pool is in dynamic equilibrium with calcium entering and exiting via the intestine, bone, and renal tubules. The skeleton turns over about 200 mg/day of calcium, but there is wide variation (Fig. 23.1).

Intestinal calcium absorption occurs through two pathways: an active, transcellular, vitamin D−dependent pathway; and a passive, paracellular diffusional process. The duodenum is the major site of calcium absorption, although absorption occurs throughout the other segments of the small intestine and the colon. The active calcium uptake from the lumen across the brush border membrane occurs through TRPV5 (Transient Receptor Potential Cation Channel Subfamily V Member 5) and TRPV6 (Transient Receptor Potential Cation Channel Subfamily V Member 6) transporters located on the apical membrane. The transport of calcium through the cytosol requires a vitamin D−inducible protein, calbindin D_{9K}. At the basolateral membrane, calcium is removed from the cell by the Ca^{2+}-ATPase (PMCA1b) and an Na^{+}/Ca^{2+} exchanger (NCX1) [3]. Each of these steps is regulated by 1,25 $(OH)_2$ D.

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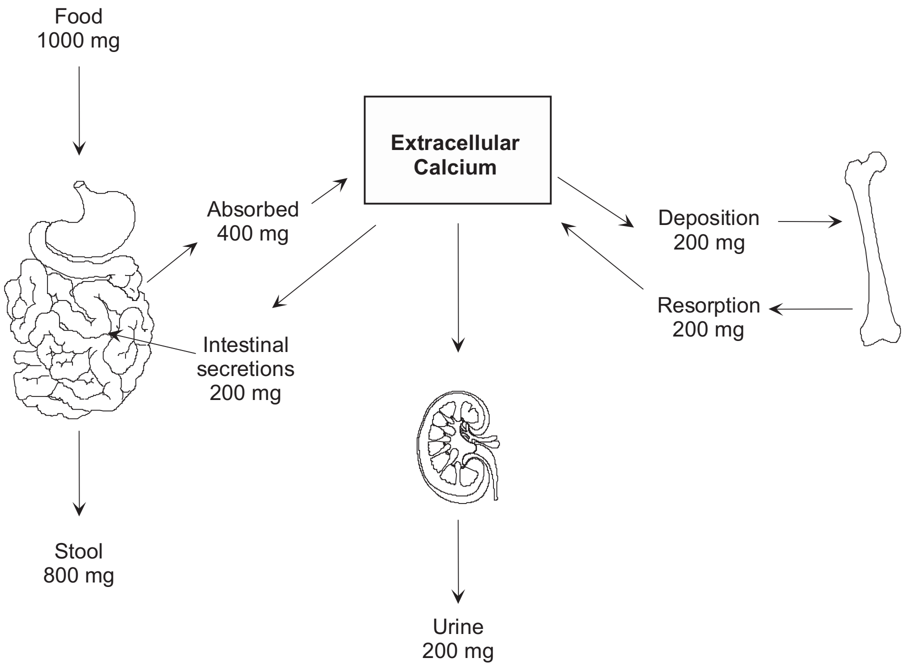

FIGURE 23.1 Diagram of calcium homeostasis showing dietary intake, the absorption and secretion of calcium by the intestine, skeletal deposition, and resorption and excretion of calcium by the kidney.

In the kidney, 60% of the filtered calcium is reabsorbed in the proximal tubule, mainly passively, through paracellular pathways via convection (solvent drag) and electrochemical gradients. Approximately 20% of calcium is reabsorbed in the thick ascending limb of the loop of Henle of which about two-thirds are paracellular and the remaining is transcellular. In addition, about 15% of the filtered calcium is reabsorbed in the distal convoluted tubule, the connecting tubule, and the initial part of the cortical collecting tubule. In this distal part of the nephron, calcium reabsorption actively opposes the natural electrochemical gradients. Luminal calcium enters the cells via the epithelial calcium channels, TRPV5 and TRPV6. Inside the cells, calcium binds with calbindin D_{28K} and is transported through the basolateral membrane via Ca^{2+}-ATPase (PMCA1b) and Ca^{2+}-Na^{+} exchangers (NCX1). This active transcellular transport is regulated by PTH, $1{,}25(OH)_2\ D_3$, calcium intake, and estrogens. PTH stimulates renal calcium reabsorption by upregulating the expression of the TRPV5, calbindin D_{28K}, NCX1, and PMCA1b [4]. Vitamin D receptor (VDR) null mice and 1-alpha hydroxylase-deficient animals show downregulation of TRPV5 and calbindin D_{28K}, demonstrating an important role of vitamin D in regulating renal calcium absorption [5]. Similarly, studies performed in VDR and 1-alpha hydroxylase knockout mice fed a high-calcium rescue diet showed upregulation of all four proteins [6]. It has also been demonstrated that estrogen upregulates the expression of TRPV5 in kidney in a $1{,}25\text{-}(OH)_2D_3$-independent manner [7].

Vitamin D

Vitamin D is a multifunctional hormone that affects many essential biological functions, ranging from immune regulation to mineral ion metabolism. Vitamin D_2 (ergocalciferol) is absorbed mainly from food, and vitamin D_3 (cholecalciferol) is produced in the skin from 7-dehydrocholesterol by ultraviolet radiation (e.g., from sunlight). Both the forms of vitamin D require further metabolism to become activated, and their respective metabolism is indistinguishable. Vitamin D is transported in the blood by the vitamin D—binding protein (DBP) to the liver, where it is hydroxylated to 25(OH)D (calcidiol), the major circulating metabolite of vitamin D. This hydroxylation is catalyzed by 25-hydroxylases, which are members of the cytochrome P450 expressed in the liver, predominantly by CYP27A1 and CYP2R1, but other hydroxylases that are components of the P450 family have also been identified [8]. The conversion of 25(OH)D to the most active form of the hormone, $1{,}25(OH)_2D_3$ (calcitriol), occurs primarily in the kidney, but also in other extrarenal sites, by the action of the CYP27B1 (25(OH) D_3 1-alpha-hydroxylase) [9]. $25(OH)D_3$ is transported to the kidney by DBP and filtered by the glomerulus. Uptake of $25(OH)D_3$ occurs by endocytic internalization in the tubular epithelial cell by a megalin-dependent mechanism [10]. 25(OH)D is hydroxylated in the proximal tubule at the 1 position by the enzyme $25(OH)D_3$-alfa-hydroxylase (CYP27B1) to form $1{,}25(OH)_2\ D_3$ (calcitriol), the active form of vitamin D. Calcitriol production may occur in many tissues and contributes to its circulating levels. Calcitriol circulates in plasma bound to DBP. Extrarenal production of CYP27B1 has been demonstrated in sarcoidosis and other conditions, resulting in hypercalcemia due to increased calcium absorption in the intestine. The source of CYP27B1 under these conditions is the macrophage [11]. Conversely, deletion or inactivation of CYP27B1 results in vitamin-dependent rickets type 1 regardless of normal intake of vitamin D.

PTH increases 1,25$(OH)_2D_3$ by inducing CYP27B1. Synthesis of 1,25$(OH)_2D_3$ can also be enhanced by low ambient calcium concentrations and phosphorus. Conversely 1,25$(OH)_2D_3$ decreases its own synthesis by inhibiting CYP27B1. In addition, FGF-23 together with its coreceptor Klotho inhibits 1,25$(OH)_2D_3$ production and increases the expression of CYP24A1, which promotes the catabolism of both 1,25$(OH)_2D_3$ and 25(OH) and leads to the production of 24,25$(OH)_2D_3$, a relatively inactive metabolite when compared to 1,25$(OH)_2D_3$ [11]. In addition, a decrease in 25(OH)D results in reduction in the pool available for 1-alpha hydroxylation [12].

1,25$(OH)_2D_3$ mediates its biological effects through its own member of the nuclear hormone receptor superfamily, the VDR, that acts as a ligand-inducible transcription factor. Ligand-bound VDR functions as a heterodimeric complex with the 9-*cis* retinoic acid nuclear receptor retinoid-X-receptor. The complex binds to target DNA sequences and regulates the transcription of several genes important in mediating the effects of vitamin D on calcium and skeletal metabolism and its diverse biological activities [13,14]. 1,25$(OH)_2D_3$ enhances the uptake of calcium in the intestine by increasing the expression of TRPV6 and the intestinal expression of calbindin. In the kidney, 1,25$(OH)_2D_3$ enhances the expression of calbindin (9 kD in intestine and 28 kD in kidney), and the expression of the Ca ATP-ase at the basolateral membrane. It also stimulates intestinal phosphorus absorption.

Other effects of 1,25$(OH)_2D_3$ include increase in bone formation and resorption. At the level of parathyroid gland, 1,25$(OH)_2D_3$ reduces PTH synthesis and secretion, decreases PTH cell proliferation, and increases the expression of the Ca receptor, thereby sensitizing the parathyroid gland to inhibition by Ca [15,16].

In CKD, 1,25$(OH)_2D_3$ production is compromised by a decrease in its synthetic apparatus in the diseased renal parenchyma, by a reduction in 25(OH) D_3 levels and by the decrease in Glomerular Filtration Rate (GFR) that further limits the delivery of 25(OH) D_3 to the site of the 1-alpha-hydroxylase in the proximal tubule [17]. Phosphate retention directly, or indirectly by inducing an increase in FGF-23, also decreases the activity of 1-alpha-hydroxylase and, therefore, 1,25 $(OH)_2D_3$ levels. Low levels of 1,25$(OH)_2D_3$ directly release the gene for PTH in the parathyroid cell from suppression by the VDR allowing an increase in PTH secretion [18]. This is aggravated by a decrease in VDR in the parathyroid cells of hyperplastic glands, which further limits the control of 1,25$(OH)_2D_3$ on PTH secretion, favoring the development and progression of SHPT. The expression of VDR is even lower in nodular hyperplasia.

Phosphate metabolism

Phosphate is an essential mineral critical for many biological processes, including bone development, cell membrane phospholipid content and function, cell signaling, and energy transfer mechanism. Abnormal phosphate metabolism is a key player in the development of the multiple mineral and bone disturbances that occur in CKD. Thus although overt hyperphosphatemia is observed late during the progression of CKD, a series of adaptive processes, including an increase in plasma FGF-23 and PTH concentrations, occur in early stages of the disease to increase phosphate excretion and maintain serum phosphate levels within a normal range. Therefore understanding phosphate balance is crucial for the interpretation of the effects that derangements in its metabolism have in mineral homeostasis, bone, and vascular tissue.

The total adult phosphorus content in the body is approximately 700 g. Precisely 80% is found in bone where it is linked with calcium to form hydroxyapatite crystals. The remainder of phosphorus is largely distributed in soft tissues, 14% intracellular, and only 10% in the extracellular space [19,20]. Plasma contains both organic and inorganic forms of phosphorus. The organic phosphorus fraction, found mainly in phospholipids, accounts for approximately two-thirds of the total plasma phosphorus. Inorganic phosphorus primarily exists as phosphate (PO_4) and is the commonly measured fraction, present in concentration between 2.5 and 4.5 mg/dL. Precisely 15% of the inorganic phosphorus is bound to plasma proteins. The rest is complexed with sodium, magnesium, and calcium or circulates as the free monohydrogen (HPO_4^{2-}) or dihydrogen forms ($H_2PO_4^{-}$). Phosphorus has a p*K*a of 6.8, and at a normal physiologic body pH of 7.4, it primarily exists as a divalent ion in a ratio of about 4:1 HPO_4^{2-} to $H_2PO_4^{-}$. The term "plasma phosphorus" is used when referring to plasma inorganic phosphorus concentration, and because plasma inorganic phosphorus is nearly all in the form of the PO_4 ion, the terms "phosphate" and "phosphorus" are often interchangeably used in clinical chemistry laboratory [21].

The concentration of phosphorus in the extracellular space is the result of the interactions among intestinal

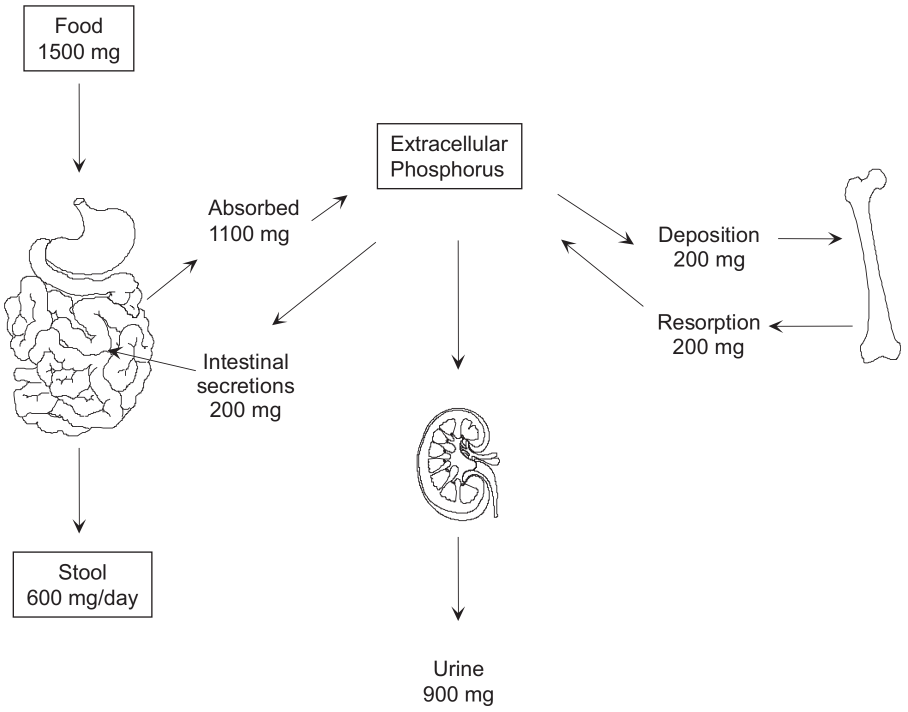

FIGURE 23.2 Diagram of phosphorus homeostasis showing dietary intake, the absorption and secretion of phosphorus by the intestine, skeletal deposition, and resorption and excretion of phosphorus by the kidney.

uptake, renal tubular reabsorption, and exchange with bone and the intracellular compartment [20] (Fig. 23.2).

Phosphate intake by adults in developed countries ranges from 1000 to 1500 mg/day. Approximately 60%−80% of dietary phosphorus is absorbed along the entire length of the intestine but is maximal in the small intestine [22,23]. Intestinal phosphate absorption is linear and nonsaturable as a function of phosphate intake. Absorption occurs via two routes: a paracellular pathway involving tight junctions and driven by a passive diffusional flux, and an active transcellular transport involving the type II sodium-dependent phosphate cotransporter Npt2b. The energy for this transport process is provided by the sodium gradient induced by the sodium−potassium ATPase at the basolateral membrane [24]. Two additional type III sodium-dependent phosphate cotransporters, PiT1 and PiT2, have been found to be expressed in the intestine. The precise role of Pit transporters remains to be determined. In NaPi-IIb-$^{-/-}$ mice, there is no residual sodium-dependent phosphate transport activity, suggesting that Pit-mediated transporters are of limited significance in the intestine [25,26]. The two major factors known to regulate Npt2b expression are dietary phosphate and 1,25(OH)$_2$D$_3$, which increases phosphate transport. Studies in both the VDR knockout mouse and the 1-alpha-hydroxylase knockout mouse have shown that Npt2b regulation by modulating dietary phosphate occurs through a vitamin D−independent pathway [25−28]. Other factors have been shown to modulate Npt2b expression, such as estrogens, glucocorticoids, epidermal growth factor, metabolic acidosis, matrix extracellular phosphoglycoprotein (MEPE), and FGF-23 [29−34].

The kidneys play a major role in maintaining phosphorus balance by excreting the net amount of the absorbed phosphorus. As phosphorus is not significantly bound to albumin, most of the phosphorus is filtered freely at the glomerulus. At steady state, 80%−90% of the filtered phosphorus is reabsorbed by the kidneys. The proximal tubule reabsorbs 70%−80% of filtered phosphorus through type II sodium−phosphate cotransporters Npt2a and Npt2c, expressed at the apical membrane of renal proximal tubule cells. The type III phosphate transporter PiT-2 has been shown to contribute to phosphate absorption in the proximal tubules. Knockout studies in mice have shown that 70% of the renal phosphate absorption is mediated by Npt2a and approximately 30% by Npt2c. Double-knockout Npt2a/Npt2c mice still exhibit some renal phosphate reabsorption, indicating a role for PiT-2 in this process [35−38]. Phosphate transport across the basolateral membrane remains a poorly understood process. Several phosphate transport pathways have been postulated, including a phosphate-anion exchanger, passive diffusion, or phosphate transport via type II sodium−phosphate cotransporters.

Several factors that stimulate renal phosphate transport include phosphate depletion, insulin-like growth factor-1, growth hormone, thyroid hormone, 1,25(OH)$_2$ vitamin D$_2$ phosphate [38−41]. Factors that inhibit phosphate reabsorption include PTH, FGF-23, phosphate loading, volume expansion, metabolic acidosis, glucocorticoids, and calcitonin [42–44]. The main hormones that regulate renal phosphate handling are PTH and FGF-23. In CKD the fractional excretion of phosphate may exceed 50% to compensate for the loss of functioning nephrons.

Parathyroid hormone

PTH is an 84-amino acid protein synthesized in the parathyroid gland and stored in secretary granules which release PTH in response to a reduction in the levels of ionized calcium, hyperphosphatemia, and/or 1,25(OH)$_2$D$_3$ deficiency. Following release, PTH 1–84 has a relatively short half-life in plasma of just minutes and is cleaved into a variety of fragments of the hormone in the liver and kidney. Several mechanisms are involved in the regulation of PTH synthesis and secretion by the parathyroid gland. Calcium sensing receptor (CaSR), the VDR, phosphate, and FGF-23 are determinants for parathyroid gland function. Calcium, the main regulator of PTH secretion, acts by the activation of the CaSR, a G protein–coupled receptor that modulates PTH secretion directly [45]. CaSR is activated by elevations in extracellular Ca concentration, leading to the inhibition of PTH, whereas low serum-ionized calcium increases PTH secretion. Vitamin D, acting through the VDR, regulates PTH by the inhibition of PTH mRNA expression. In addition, 1,25(OH)$_2$D$_3$ has an indirect suppressive effect on PTH, by increasing intestinal Ca absorption.

In CKD, low serum calcium, resulting from decreased intestinal calcium absorption due to low 1,25(OH)$_2$D$_3$ levels, leads to an increase in PTH secretion. Studies in experimental animals indicate that signal transduction via the CaSR is a determinant of parathyroid cell proliferation and can lead to parathyroid gland hyperplasia [45]. Studies show that parathyroid cells from parathyroid hyperplasic tissue are less sensitive to the inhibitory effect of calcium [46]. Other studies in normal rats and rats with CKD indicate that parathyroid cell hyperplasia is associated with a decrease in CaSR and VDR expression. Furthermore, resected parathyroid glands from patients with severe SHPT have nodular areas throughout the gland that represent monoclonal expansion of parathyroid cells. These cells have reduced the expression of CaSR and VDR, which decreases their sensitivity to the inhibitory effects of calcium and 1,25(OH)$_2$D$_3$ on PTH secretion and consequently favors more severe SHPT [47]. A direct consequence of these alterations is an increased difficulty in controlling PTH levels in patients with SHPT and enlarged parathyroid glands.

The precise mechanism of the regulation of PTH secretion by phosphate is not completely understood. Hyperphosphatemia may affect the regulation of intracellular Ca in parathyroid cells, resulting in the inhibition of phospholipase A2 (PLA2) and diminished synthesis of arachidonic acid (AA) formation, the latter being a potent inhibitor of PTH release [48]. Hyperphosphatemia is also associated with reduced expression of the CaSR, thereby decreasing the ability of the parathyroid gland to respond to changes in ionized Ca [49]. In addition, high phosphate intake induces parathyroid cell proliferation and growth through transforming growth factor alpha (TGF-α), mediated via the epidermal growth factor receptor, resulting in parathyroid hyperplasia and the development of SHPT [50,51].

In the kidney, PTH binds to type I PTH receptor in proximal tubular cells [52] and thereby activates cyclin adenosine monophosphate (cAMP)-protein kinase A and the phospholipase C-protein kinase C signal transduction pathways. Activation of both signaling pathways leads to the internalization of the sodium–phosphate cotransporters Npt2a and Npt2c, leading to increased phosphate excretion. The removal of Npt2a from the apical brush border membrane in response to PTH requires the presence of the sodium–proton exchanger regulatory factor 1. After the removal of the exchanger from the brush border in response to PTH, Npt2a is sent to early endosomes and then to lysosomes, where subsequent proteolytic degradation of the transporter occurs [43,53,54].

Measurement of PTH levels

Measurement of plasma PTH is essential for the assessment of abnormalities in PTH secretion, and particularly the assessment of disturbances in bone and mineral metabolism in the setting of CKD. Measurement of PTH has been complicated by the existence of circulating PTH fragments and their recognition by particular hormone assays, and a lack of standardization of the assays. PTH assays have evolved from first generation, in which a polyclonal antibody was used for the recognition of circulating PTH, to a second generation using two specific antibodies to the carboxy-terminus and amino-terminus portion of the hormone, respectively, with the ability to capture the 1–84 molecule. However, these assays also recognize 7–84, a fragment that frequently circulates in patients with CKD, resulting in overestimation of the PTH level [55]. Third-generation assays use more specific antibodies against the N-terminal portion of the molecule and, thus, are able to capture the whole PTH molecule [56,57]. Comparisons between second- and third-generation assays have given good results [58], but the difference between results become significant as PTH levels increase. The interpretation of the PTH assay is important from the clinical stand point because current guidelines deal with plasma PTH levels. The guidelines make recommendations for treatment based on trend monitoring, the use of a fold-increase of the upper reference limit [1,2], or cutoffs for initiating or stopping treatment in patients with CKD. Therefore it is important to take into account what PTH assay is used to monitor the patient and to make clinical decisions [59].

Fibroblast growth factor-23 and Klotho

The term "phosphatonin" was originally described as a circulating factor that caused renal phosphate wasting in patients with tumor-induced osteomalacia (TIO), a paraneoplastic syndrome characterized by renal phosphate wasting, aberrant vitamin D metabolism, and osteomalacia. Search for phosphatonin in patients with TIO led to the identification of FGF-23. In addition to FGF-23, other identified phosphatonins include secreted frizzled-related protein 4, MEPE, and FGF-7 [60−67]. FGF-23 is the bone-derived phosphatonin that has been extensively studied and has been found to play a critical role in normal physiology and altered mineral metabolism in CKD.

FGF-23 is a 32-kDa, 251 amino acid protein, predominantly expressed in osteocytes and osteoblasts in the skeleton, but low levels of unclear significance can be found in pericyte-like cells that surround the venous sinusoids of the bone marrow, ventrolateral thalamic nuclei, heart, thymus, and small intestine [68,69].

The kidney is the main target organ for FGF-23. Injection of recombinant FGF-23 into animals induces a rapid decline in renal phosphate reabsorption, resulting in hypophosphatemia, low serum calcitriol levels, and bone demineralization. FGF-23 activates FGF receptors on the basolateral membrane of the renal tubules resulting in decreased expression of Npt2a and Npt2c on the apical surface of the tubular cell. The reduction in the number of Npt2a by FGF-23 seems to be independent of PTH [70]. FGF-23 also suppresses the 1α-hydroxylase enzyme (CYP27B1) in the renal tubule, the enzyme that stimulates the conversion of 25-hydroxyvitamin D to $1,25(OH)_2D$. FGF-23 also enhances the expression of 24-hydroxylase (CYP24), which converts $1,25(OH)_2D$ to inactive metabolites in the proximal renal tubules [26,71,72]. FGF-23 exerts its biological functions by binding to the Fibroblast Growth Factor Receptor, (FGFR), which requires full-length Klotho as coreceptor, a type I membrane receptor with homology to beta-glycosidases [73,74]. The transmembrane and secreted forms of Klotho proteins may collectively affect the aging process in mammals [75].

Klotho expression is restricted to a few tissues, including the distal convoluted tubules in the kidney, parathyroid glands, the sinoatrial node, the pituitary gland, and the choroid plexus in the brain. It is still unclear how FGF-23 exerts its physiological effects on the proximal tubule in the kidney since Klotho appears to be expressed in the distal tubular epithelial cells. It has been shown that Klotho is expressed at the cell surface, but its extracellular domain could be shed by secretases and released into the circulation to act as an endocrine factor. In the kidney, FGF-23 binds to the complex FGFR-Klotho to activate extracellular signal-regulated kinases and serum/glucocorticoid-regulated kinase, which ultimately leads to the downregulation of membrane expression of the sodium transporter NaPi-2A, resulting in an increase in urinary phosphate excretion [76,77]. Klotho also may undergo cleavage at the cell surface and release to the circulation and may directly regulate calcium and phosphorus excretion in the kidney, 1-alpha hydroxylase activity, PTH, and FGF-23 [78,79]. In Klotho-deficient mice the FGF-23 concentration is increased but is ineffective in controlling serum phosphate levels. In conclusion, Klotho is a coreceptor that specifically increases the sensitivity of FGF receptors to FGF-23 [54,73,74,80].

Under conditions of Klotho deficiency in the renal tubule, there is a decrease in the phosphaturic effect of FGF-23 [81]. Low Klotho expression has been observed in kidneys of patients with CKD stage 1, and Klotho expression decreases progressively as CKD advances. This decrease in Klotho is followed by reduction in $1,25(OH)_2D_3$, and increase in serum FGF-23 and intact PTH, which becomes significant in stage 3 CKD [79]. A result of the decrease of Klotho as renal function declines is a loss of the negative feedback for FGF-23 secretion by the osteocyte and an increase in FGF-23 levels, which allows FGFR activation independent of Klotho. This leads to an increase in the fractional excretion of phosphate, which would, in turn, lead to the normalization of serum Pi levels despite falling renal Klotho expression. In advanced CKD, by contrast, levels of Klotho are not sufficient to support renal FGF-23-Klotho signaling; thus FGF-23 cannot compensate for the renal failure−induced P retention. Consequently, elevated serum phosphate becomes the main regulator of FGF-23 in advanced CKD [78]. In conclusion, Klotho is a coreceptor that specifically increases the sensitivity of FGF receptors to FGF-23 [54,73,74,80] and seems to play a role in the pathogenesis of the early changes in renal phosphate handling in CKD.

Since renal Klotho starts to decline in mild CKD and precedes elevations of FGF-23, it has been suggested that Klotho levels can be utilized as surrogate markers for renal Klotho and as a sensitive early marker of loss of renal function. However, preclinical animal data indicate that Klotho deficiency is not just merely a biomarker, but a pathogenic factor for CKD progression and extrarenal CKD complications, including cardiovascular disease (CVD) and disturbed mineral metabolism.

Besides its effect on tubular phosphate handling, FGF-23 may affect PTH synthesis and secretion. Injection of FGF-23 in animals rapidly decreases PTH secretion, within 10 minutes, through the Mitogen Activated Kinase (MAPK) pathway; FGF-23 also inhibits PTH gene expression in parathyroid glands. In addition, FGF-23 increases 1-alpha-hydroxylase expression in bovine parathyroid cells, which may contribute to the reduced PTH gene transcription [54,82,83].

FGF-23 gene expression in bone is regulated by phosphate and $1,25(OH)_2D_3$. Phosphate loading in mice increases FGF-23 levels, but the data in humans are conflicting. Some studies fail to demonstrate an increase in serum FGF-23 levels in response to phosphate loading, whereas phosphate restriction has been associated with a small, but significant, decrease in circulating FGF-23 levels. Extracellular phosphorus did not directly stimulate FGF-23 mRNA levels or FGF-23 gene promoter activity in osteoblastic cultures [84−88]. $1,25(OH)_2D_3$ stimulates FGF-23 production both in vivo and in vitro. This effect seems to be mediated through the VDR since VDR-null mice did not show an increase in FGF-23 levels in response to $1,25(OH)_2D_3$ administration. FGF-23 secretion is also regulated by local bone-derived factors, such as phosphate-regulating gene with homologies to endopeptidases on the X chromosome (PHEX) and dentin matrix protein 1 [68,89]. $1,25(OH)_2D_3$ is also able to suppress PHEX mRNA levels in bone cells, and reductions in PHEX can increase FGF-23 expression in osteocytes. Therefore it is plausible that $1,25(OH)_2D_3$ upregulates FGF-23 production in part indirectly by the downregulation of PHEX expression [90−94].

Alterations in mineral metabolism in CKD

Phosphate retention begins at an early stage of CKD, due to a gradual decline in filtered phosphate load. However, serum phosphate is maintained within normal limits until the GFR falls to less than approximately 30 mL/min [22,95]. As renal function declines, serum phosphate levels are maintained by reducing phosphate reabsorption in the remaining nephrons by FGF-23. However, this effect is limited due to proximal tubule Klotho deficiency occurring early in the course of CKD [18,79,96]. As a consequence, serum PTH increases to further reduce tubular phosphate reabsorption and maintain phosphate balance. As renal insufficiency continues to progress, FGF-23 and PTH are no longer enough to maintain phosphate homeostasis, and hyperphosphatemia develops. Both phosphate and FGF-23 inhibit 1-alpha-hydroxylase in the kidney leading to a decrease in $1,25(OH)_2D_3$ synthesis and the development of $1,25(OH)_2D_3$ deficiency. Phosphate increases serum PTH independent of serum calcium and $1,25(OH)_2D_3$ (calcitriol). In addition, calcitriol deficiency decreases intestinal calcium absorption leading to hypocalcemia, and diminished tissue levels of VDRs, which in the parathyroid gland results in resistance to calcitriol-mediated regulation and elevation of PTH secretion. All these factors lead to SHPT. As these alterations continue, nodular hyperplasia of parathyroid gland occurs, and the physiological mechanisms controlling PTH secretion become ineffective. The persistent actions of elevated PTH increase bone turnover, resorption and frailty, and consequently elevated fracture risk [18].

Because $1,25(OH)_2D_3$ is also a potent inducer of Klotho expression in the kidney, decreased levels of $1,25(OH)_2D_3$ reduce Klotho expression. FGF-23 suppresses PTH release via stimulating the dimeric Klotho-FGF receptor at the parathyroid glands, but resistance to the effect of FGF-23 appears as kidney function declines because of decreased Klotho expression in the parathyroid glands and kidney. Thus as renal function continues to decline, hyperphosphatemia develops progressively due to insufficient renal excretion despite high serum levels of PTH and FGF-23. Increased bone resorption in response to chronically elevated PTH levels can also contribute to the hyperphosphatemia observed in CKD and end-stage renal disease patients [97−101].

The effects of hyperphosphatemia are multifactorial. They include (1) a decrease in serum calcium levels through physicochemical binding; (2) suppression of 1-alpha-hydroxylase activity, resulting in decreased levels of $1,25(OH)_2D$, which causes direct increase in PTH secretion; (3) a direct effect of phosphorus on parathyroid gland cells stimulating PTH secretion, independent of serum calcium and $1,25(OH)_2D$ [48,102,103]; (4) inhibition of PLA2 and the formation of AA, a potent inhibitor of PTH release [104]; and (5) a reduction in the expression of the CaSR (calcium-sensing receptor), thereby decreasing the ability of the parathyroid gland to respond to changes in ionized calcium [49]. In addition, high phosphate intake induces cell growth by increasing the expression and actions of TGF-α which are mediated through the epidermal growth factor receptor; this worsens parathyroid hyperplasia and the resultant SHPT [50]. The effect of phosphate on PTH gene expression involves changes in the cytosolic proteins in the parathyroid gland that bind to the PTH mRNA 3′ untranslated region and determine PTH mRNA stability. Further studies have shown decreased PTH mRNA degradation in animals with uremia [105,106].

Phosphate and cardiovascular disease

Although a causal relationship between serum phosphate levels and poor clinical outcomes has not been demonstrated, concern about this association has increased the interest in reducing serum phosphate levels as a means to control cardiovascular (CVS) mortality. KDIGO guidelines suggest lowering elevated serum phosphate levels toward the normal range in CKD 3–5D (2C), and that decisions about phosphate-lowering treatment should be based on progressively or persistently elevated serum phosphorus [2].

Numerous studies have shown, that in addition to its central role in SHPT, there is an association between high phosphate levels and CVS and all-cause mortality in patients with advanced CKD [13,14,19,21,22] and also in the general population. Indeed, epidemiologic data suggest that higher serum phosphate levels are associated with increased CVS morbidity and mortality in both the general and CKD populations. The Framingham Offspring Study evaluated 3368 participants with no history of CKD or CVD and found that serum phosphate levels greater than 3.5 mg/dL were associated with an estimated 55% increased CVD risk [107]. In a post hoc analysis of the Cholesterol and Recurrent Events study, participants with serum phosphate greater than 4 mg/dL had a 50% greater risk of myocardial infarction [hazard ratio (HR), 1.50; 95% confidence interval (CI), 1.05–2.16] and a 43% greater risk of developing heart failure (HR, 1.43; 95% CI, 0.95–2.14) compared with those with serum phosphate of 2.5–3.4 mg/dL. Each 1 mg/dL higher serum phosphorus level was associated with a 27% increased risk for all-cause mortality (HR, 1.27; 95% CI, 1.02–1.59) [108]. The relationship between phosphate excess and CVS risk has also been studied in CKD patients. In a study of 3490 veterans with CKD stage 3–4, each 1-unit increase in serum phosphate was associated with a significant 35% increased risk for acute myocardial infarction (HR, 1.35; 95% CI, 10.9–1.66) and a 23% greater risk of mortality (HR, 1.23; 95% CI, 1.12–1.36) after adjustments for comorbid conditions [109].

Another large prospective longitudinal study performed in nondialyzed CKD patients was the Chronic Renal Insufficiency Standards Implementation Study, which involved 1203 patients. In CKD stages 3–4 patients, all-cause and CVS mortality risk increased as serum phosphorus increased [110]. Phosphate was initially identified as a CVS risk factor in dialysis patients in 1998 in a cohort of 6407 hemodialysis patients, followed by another study done in 2004 in 40,538 patients from the US Renal Data System, where there was a linear association of higher serum phosphate concentrations with a greater risk of CVS hospitalizations [111,112]. In another study conducted in 14,829 hemodialysis patients, the fully adjusted risk of CVS events was greater with incrementally higher serum phosphate concentrations [113].

Multiple studies performed in dialysis patients confirm the association of higher serum phosphate levels with mortality, although there were slight differences in the inflection point (the point at which the serum phosphate level becomes significantly associated with increased all-cause mortality) that varied from 5.0 to 5.5 mg/dL [112], greater than 5.5 mg/dL [114], 6.0 to 7.0 mg/dL [115], and greater than 6.5 mg/dL [116].

The mechanisms underlying the increase in CVS morbidity and mortality associated with disturbances in phosphate metabolism are not fully understood but may involve direct effects of increased phosphate on renal bone disease and vascular calcification, as well as modulation of circulating serum hormones, such as FGF-23, PTH, and calcitriol. Serum phosphate levels are also associated with CKD progression and left ventricular hypertrophy, which may contribute to CVD and death [117–119]. High FGF-23 levels were found to be an independent predictor of mortality in both incident and prevalent dialysis patients [120–123]. These effects are independent of serum phosphate, and the correlation between high serum FGF-23 and mortality remains significant even in patients with normophosphatemia. Thus even in the general population, serum FGF-23 is associated with increased mortality [117]. It is unclear whether increased FGF-23 levels are directly toxic or are a surrogate marker of the toxicity of other factors that are implicated in the development of vascular disease. Several studies demonstrate that high FGF-23 levels are associated with impaired vasoreactivity and arterial stiffness, increased left ventricular mass index, and increased prevalence of left ventricular hypertrophy in CKD patients [120,124–126]. FGF-23 is also associated with congestive heart failure [127].

Experiments in animals have shown direct cardiac effects of FGF-23 on the hypertrophy, contractility, and arrhythmic potential of the myocardium [128,129], and indirect effects on the heart by activation of the renin–angiotensin system and promotion of sodium reabsorption in the distal tubule of the kidney. It has been hypothesized that elevation of FGF-23, while necessary to control phosphate and vitamin D homeostasis, may also contribute to the development of CVD [127].

Another possible mechanism by which phosphate may influence CVS risk is by stimulating PTH secretion and inhibiting the activation of vitamin D. PTH excess and 1,25(OH)$_2$D deficiency are associated with increased CVS risk in some observational studies. Calcitriol potentially suppresses the renin–angiotensin–aldosterone system and regulates cardiomyocyte proliferation and hypertrophy [111,112,130,131]. FGF-23 inhibits 1-alpha-hydroxylase in the kidney, resulting in decreasing

1,25-dihydroxyvitamin D synthesis. Further studies are needed to identify if phosphate increases CVD through a mechanism that involves vitamin D. Regardless of the underlying mechanisms, it is important to consider phosphate levels as a key factor in the generation of CKD-mineral and bone disorder (CKD-MBD).

Phosphate and vascular calcifications

Vascular calcification has been recognized as a common complication of CKD for many years. Calcium phosphate deposition is the hallmark of vascular calcifications and can occur in blood vessels, myocardium, and cardiac valves. There are two types of arterial calcifications. Intimal calcification occurs within atherosclerotic plaques. Arterial medial calcification or Monckeberg's sclerosis occurs at the internal elastic lamina of the media layer. This type of vascular calcification is more common in patients with CKD, diabetes mellitus, and advanced aging. Similar to intimal calcification, the presence of arterial medial calcification is a powerful and independent prognostic marker for all cause and CVS mortality in end-stage renal disease patients [132].

The presence of atherosclerotic vascular disease is often associated with the development of plaques and occlusive lesions. Medial wall calcification is known to be associated with increased arterial stiffness and reduced vascular compliance, and increased pulse wave velocity. These hemodynamic changes lead to left ventricular hypertrophy, compromised coronary blood flow during diastole, and increased CVS and all-cause mortality. Arterial medial calcification can also involve the small arterioles of the skin, causing calciphylaxis, a condition associated with extremely high mortality rates in dialysis patients [133,134].

Vascular calcification can be detected by a number of radiologic techniques. Plain radiography is the simplest technique used to detect the presence or absence of vascular calcification. Although some degree of differentiation between medial and intimal calcification can be detected on plain radiographs, this technique is insensitive and difficult to quantify [132]. Other techniques that have been used include vascular ultrasonography which can identify calcified plaques and calcified media, and intravascular ultrasonography, a more accurate technique that allows for the measurement of absolute cross-sectional luminal areas [135,136]. For coronary artery calcifications, other noninvasive techniques such as tomography-based approaches [electron beam CT (computerized tomography) (EBCT) and multislice CT] permit assessment and quantification of the extent of calcifications. Braun et al. reported that EBCT has a sensitivity of 93% and a specificity of 73% when angiography was used as the reference standard. These CT-based techniques do not allow differentiating atherosclerotic calcifications and medial calcification [133,137].

Bellasi et al. compared different simple, noninvasive techniques to detect calcification with those obtained using electron beam tomography (EBT) for coronary artery calcium (CAC) scoring in 140 prevalent hemodialysis patients [138]. All patients underwent EBT imaging, a lateral X-ray of the lumbar abdominal aorta, an echocardiogram, and measurement of pulse pressure (PP). Calcification of the abdominal aorta was scored as 0−24 divided into tertiles, echocardiograms were graded as 0−2 for the absence or presence of calcification of the mitral and aortic valve, and PP was divided in quartiles. The likelihood ratio (95% CI) of coronary artery calcification score by an EBCT of greater or equal to 100 was 1.79 (1.09, 2.96) for the calcification of either valve and 7.50 (2.89, 19.5) for participants with a lateral abdominal radiographic-score greater or equal to 7. In contrast, no association was present between PP and EBCT calcification score [138]. KDIGO guidelines recommend the use of plain lateral abdominal radiography or echocardiography to detect the presence or absence of coronary artery calcification in end-stage renal disease patients [1].

The prevalence of vascular calcifications varies according to age, method of detection, site of measurement, time on dialysis, and diabetic status. Goodman et al. found that coronary artery calcification occurs more frequently in young dialysis patients (between 20 and 30 years of age) compared to either normal subjects of the same age and sex or older adults with normal renal function [139]. Another study showed that coronary artery calcification by EBCT increased with advancing age in patients on dialysis and that the calcification scores were two to fivefold higher in the dialysis patients than in age-matched nondialysis patients with angiographically proven coronary artery disease [137]. An autopsy study done in 54 cases was designed to compare morphology and immunohistology of coronary arteries and coronary plaques of patients with End Stage Renal Disease (ESRD) and matched nonrenal patients who had died from a cardiac event. The magnitude of atherosclerotic plaque burden and intimal thickness in the dialysis patients was similar to the nonuremic controls. Coronary plaques in patients with end-stage renal disease were characterized by increased media thickness and marked calcification [140]. The prevalence of detectable coronary and peripheral artery calcifications in dialysis patients ranges from 30% to 92%, according to age, sex, dialysis duration, and site of measurement [137,141,142]. The earliest and commonest site of calcification is the ankles, followed in frequency by the abdominal aorta, feet, pelvis, and hands and wrists in radiographs. Valvular calcifications are also common in dialysis patients. EBCT studies showed a prevalence of 45%–59% in the mitral valve and 34%–55% in the aortic valve [137,143].

There are limited data concerning the prevalence of coronary artery calcification using CT in CKD patients not yet on dialysis. Kramer et al. evaluated the association between CKD and coronary artery calcification among 2660 patients in the Dallas Heart Study aged 30–65 years. No association was noted between stages 1 and 2 CKD and increased coronary artery calcification scores. Compared with no CKD, stages 3–5 CKD were associated with increased risk of having increased coronary artery calcification, particularly very high calcification scores. This was largely due to the inclusion of patients with diabetes as there was no significant association between increased coronary artery calcification scores and the nondiabetic population who had stages 3–5 CKD [144].

Several studies demonstrate that coronary artery calcification is associated with increased mortality in dialysis patients. In a prospective study conducted in 110 dialysis patients, the authors correlated the amount of baseline vascular calcification (as assessed by ultrasonography at four different anatomic sites) with survival during a period of more than 4 years of follow-up. The results of this study showed that the presence and extent of vascular calcifications were strong predictors of CVS and all-cause mortality [145].

One study followed 127 incident hemodialysis patients prospectively after baseline EBCT and demonstrated that the severity of coronary artery calcification at the time of initiation of hemodialysis is an important predictor of long-term survival. Even after adjustment for age, race, gender, and diabetes, a baseline CAC greater than 400 was associated with a greater than fourfold increase in mortality [146].

Hyperphosphatemia has been linked to arterial calcifications in several human observational studies and in cell culture models. In a small study of dialysis patients, the mean serum phosphorus concentration was higher among the patients with coronary artery calcification [139]. Adeney et al. evaluated 439 participants from the Multi-Ethnic Study of Atherosclerosis who had moderate CKD and no clinical CVD. After adjustment for demographics and estimated GFR, each 1 mg/dL increment in serum phosphate concentration was associated with a 21% ($P = .002$), 33% ($P = .001$), 25% ($P = .16$), and 62% ($P = .007$) greater prevalence of coronary artery, thoracic, aortic valve, and mitral valve calcification, respectively [147]. The relationship between serum phosphate levels and vascular calcification was also evaluated in the general population. In 3015 healthy young adults in the prospective Coronary Artery Risk Development in Young Adults study, phosphorus levels were measured at baseline, and the presence of CAC was assessed by computed tomography 15 years later. Serum phosphate levels greater than 3.9 mg/dL had a 52% greater risk of coronary artery calcifications as compared with those with a phosphate level less than 3.3 mg/dL (adjusted OR, 1.52; 95% CI, 1.04–2.22) [148]. High serum phosphate level was also found to be associated with vascular stiffness in the general population. The association between serum phosphorus levels and arterial stiffness as estimated by an ankle brachial pressure index (ABPI) was examined in 581 participants with normal renal function in the third National Health and Nutrition Examination Survey. There was a strong association between the highest quartile of serum phosphorus (3.7–5.0 mg/dL) and high ABPI compared to the reference group (3.1–3.4 mg/dL) after multivariate adjustment (adjusted OR, 4.78%;95% CI, 1.73–13.2; $P = .003$) [149,150]. The findings from previous studies suggest that high serum phosphate levels are a risk factor for the development of vascular calcifications. Lowering serum phosphate levels with a noncalcium-based phosphate binder was found to slow the progression of vascular calcification in end-stage renal disease patients [151,152]. Several animal studies pointed to a role of elevated phosphorus in vascular calcification. Uremic rats treated for 3 months with a high-phosphate diet showed aortic medial calcification that was decreased by treatment with the noncalcium phosphate binder, sevelamer [153].

Vascular calcification is a highly regulated process and occurs as a result of (1) phenotypic transformation of vascular smooth muscle cells (VSMCs) into osteochondrogenic-like cells, (2) the stimulation of these cells to actively synthetize mineralization-initiating matrix vesicles, (3) VSMC apoptosis with the release of calcifying apoptotic vesicles, and (4) an imbalance of systemically and locally produced promoters and inhibitors of mineralization.

Several studies have described the ability of serum phosphorus to potently stimulate the phenotypic transformation of VSMCs into osteoblasts capable of producing a promineralizing milieu. In a hyperphosphatemic environment ($Pi > 2.4$ mM), the VSMC culture systems revealed both osteochondrogenic phenotypic change and mineralization through the sodium-dependent phosphate transporter, Pit-1. These in vitro and animal experiments demonstrate that phosphate plays a key role in controlling vascular calcification [154–156].

In addition to vascular calcification, heart valve calcification occurs with a higher prevalence and at lower age in CKD compared with non-CKD patients and carries an increased risk of death and other clinical consequences [143,157–159]. Indeed, in a recent analysis of several publications comprising more than 600 patients, it was shown that in CKD patients the prevalence of calcification varied between 25% and 59% in the mitral valve, and 28% to 55% in the aortic valve [160]. There is an association between serum phosphate concentrations and aortic and mitral valve calcification [160,161]. In addition, the extent of aortic valve calcification has been associated with FGF-23, hyperparathyroidism, and sclerostin [162].

Control of serum phosphate in CKD

In 2003 the National Kidney Foundation released the Kidney Disease Outcomes Quality Initiative (KDOQI) clinical practice guidelines for bone metabolism and disease in CKD. KDOQI recommended targeting serum phosphorus levels at 2.7−4.6 mg/dL in patients with CKD stages 3 and 4 and 3.5−5.5 mg/dL in those with CKD stage 5D. In contrast, KDIGO guidelines from 2017 reaffirmed the need to decrease serum phosphate levels in CKD 3−5D toward the normal range.

As discussed previously, during the early stages of CKD, a rise in serum FGF-23 and PTH maintains serum phosphate levels within the normal range. Therefore a relative reduction in phosphate intake seems logical as a mean to decrease the amount of phosphate absorbed in the intestine and consequently, to decrease FGF-23 and PTH secretion. Indeed, in early experimental studies done in uremic dogs, dietary phosphorus reduction in proportion to the reduction in GFR was effective in preventing the development of hyperparathyroidism during a period of 2 years of observation, suggesting a critical role for phosphate retention in the elevation of PTH [163]. However, in clinical terms, the use of phosphate-lowering agents at these stages of CKD is highly controversial as there is no hard evidence of better outcomes in terms of SHPT [2]. In addition, the determination of the amount of phosphate binders required is difficult, because serum phosphate levels at these stages will not express the state of phosphate balance. Alternative biomarkers, such as FGF-23 or urinary phosphate excretion, may become important measures of altered phosphorus metabolism not reflected in serum levels and may indicate the need for treatment in earlier stages of CKD, before the onset of hyperphosphatemia.

In CKD stages 5 and 5D, increases in serum FGF-23 and PTH are not sufficient to control phosphate levels. As discussed later, counseling on nutritional recommendations to reduce phosphate intake by diminishing protein consumption and adequate selection of the protein source (animal vs vegetable, food additives, medications, etc.) are central to the management of phosphate burden [164,165]. However, patient's compliance frequently limits the effectiveness of protein-restricted diets in reducing phosphate burden and the control of hyperphosphatemia. Furthermore, controversy exists as to the extent of dietary protein restriction in patients with advanced renal disease in which nutritional status may be already compromised by the disease. Hence, most patients will require the use of phosphate binders to decrease intestinal absorption and dialysis therapy to remove phosphorus from the body. Despite these measures, less than 50% of dialysis patients meet target levels for serum phosphorus [166]. In another study conducted in 1814 CKD patients (SEEK study), only 15% of patients had a serum phosphate level less than 4.6 mg/dL when their GFR was 20−29 mL/min [95]. The multifactorial reasons for the suboptimal phosphate control include late referral to a nephrologist with subsequent late start of dietary phosphate restriction and fear that tight phosphate restriction may represent a risk for protein malnutrition. Once counseling for phosphate-lowering is initiated, other challenges appear, including poor adherence to dietary restrictions, the phosphate binder pill burden, and the cost of the phosphate binders. Hence, solid knowledge of phosphorus content of different foods is essential to the clinical management of patients with advanced CKD.

Dietary phosphorus restriction

Several studies have examined the effects of dietary phosphate restriction on abnormalities of bone and mineral metabolism, progression of renal dysfunction, and mortality. In patients with advanced CKD, where urinary phosphate excretion is severely impaired, dietary absorption becomes a critical determinant of serum phosphate concentrations. Hemodialysis patients absorb approximately 60% of dietary phosphorus, compared with about 80% absorption in healthy volunteers consuming an identical study meal. The use of activated vitamin D analogs further increases intestinal phosphorus absorption [167].

Since phosphorus exists in virtually all living organisms, it is found in most foods. Dietary sources of phosphorus include the organic phosphorus found in foods high in protein, such as meat, dairy products, eggs, grains, legumes, nuts, and inorganic phosphorus found in food additives and preservatives. Table 23.1 shows a partial list of the phosphorus content in different group of foods.

Any strategy to control dietary phosphorus intake in CKD patients must consider the actual content of phosphorus in food, as well as the bioavailability of phosphorus from various food sources. Organic

TABLE 23.1 Phosphorus content of selected foods (US Department of Agriculture, (USDA)).

Food	Portion size	P (mg)	Protein (g)	P/protein
Chicken	140 g	286	43	6.65
Turkey	3 oz	208	24	8.7
Beef	3 oz	200	26.4	7.6
Pork	3 oz	224	22	7.4
Veal	3 oz	212	31	6.8
Lamb	3 oz	167	22	7.4
Fish	3 oz	230	20.23	11.36
Crab	3 oz	240	16.5	14.5
Egg (whole)	1 large	99	6.29	15.7
Egg (white)	1 large	5	3.6	1.4
Cheese	1 oz	133	6.6	20
Milk	1 cup	222	7.9	28
Bread	1 slice	25	3.4	7.3
Cereals	1 cup	259	5.2	49.8
Peanuts	1 oz	101	6.7	15.1
Almonds	1 oz	134	6	22.3
Beans	1 cup	183	12	15
Lentils	1 cup	356	17.9	19.9
Rice, white	1 cup	74	4	18.4
Rice, brown	1 cup	162	5	32

phosphorus in animal proteins is hydrolyzed in the intestinal tract and then absorbed into the circulation as inorganic phosphate [168]. Usually, 40%–60% of organic phosphate in animal proteins is absorbed in the gastrointestinal tract. By comparison, plant-derived phosphorus from seeds, legumes, or nuts is less easily absorbed because it is in the form of phytic acid or phytate. Because the human intestine does not secrete phytase, the enzyme required for digestion of phytate and absorption of the phosphorus bound to phytate, the bioavailability of phosphorus from plant-derived food is usually less than 50% [169].

Inorganic phosphorus and food additives

Phosphorus is the main component of many food additives and preservatives. Phosphorus-containing additives, the most rapidly growing source of dietary phosphorus over the past two decades, are increasingly being added to processed foods, such as enhanced meats, processed or spreadable cheeses, frozen meals, baked products, and beverages. These phosphate salts are used to extend shelf life, to preserve moisture or color, and to enhance flavor. The phosphate additives found in different preparations (e.g., sodium phosphate, potassium phosphate, calcium phosphate, phosphoric acid, and various pyrophosphates and polyphosphates) are not protein-bound and are more readily available for absorption, being almost 100% absorbed [170,171]. Since 1990, phosphorus-containing food additives in the general US population have doubled and will probably continue to increase as the American demand for convenience and fast food escalates. Depending on individual food choices, phosphorus intake from additives could contribute up to 1 g/day [172,173]. The contribution of inorganic phosphorus from processed foods was determined in an experiment performed with eight graduate students who participated in a randomized, crossover study where two dietary patterns were fed. For one 4-week period, volunteers were fed commercial foods free of phosphate additives; during the second 4-week period, they were fed commercially available foods very similar to those in the control diet, but containing phosphate additives (e.g., processed cheese instead of natural cheese, meats with added phosphates instead of fresh meats, and colas rather than citric acid–containing soft drinks). These substitutions increased the dietary phosphorus intake by an average of 1154 mg/day while keeping the intake of protein and calcium unchanged [174,175].

Soft drink manufacturers add different amounts of phosphate to the beverages to enhance flavor. Many but not all clear-colored beverages or teas are low in phosphate. Table 23.2 shows the phosphorus content of some commonly used beverages [66,176].

Another source of dietary phosphorus which has become increasingly recognized in the literature and may increase the total phosphorus content is the "enhancement" of meat and dairy products. Uncooked meat and poultry products are frequently enhanced

TABLE 23.2 Phosphate content (mg) of selected beverages (based on 12 oz serving).

Beverage	Phosphate (mg)
Coke	69.9
Pepsi-Cola	57
Diet Cherry Coke	56
Diet Pepsi	50
Dr. Pepper	45
Hires Root Beer	22
Fruitworks	53–140
Gatorade	36
Tropicana Fruit Drinks	37–93

by food processors using sodium and potassium phosphate salts. Enhanced meat and poultry products may increase phosphorus and potassium content by almost two- to threefold, respectively [177]. The federal guidelines require manufactures to include a statement of enhancement with specifications of the additives used, but they are not quantified, and many consumers are not aware that they are purchasing an altered product. Phosphate salts are also used in ham and bacon to improve color and flavor, and to reduce oxidation and stabilize proteins. Different types of cheese contain various amounts of phosphorus, from less than 100 mg (e.g., Brie cheese) to almost 1000 mg per serving of combined organic and inorganic phosphorus in processed soft cheese [20,171,176].

Prescription medications may also be a source of phosphorus that contributes to phosphate intake. In a recent study from a total 1744 drug formulations of 124 different medications, 185 (11%) contained a phosphate salt. Central nervous system (CNS) and CVS medications accounted for 65% and 24% of phosphate-containing medications, respectively. Precisely 30% of Hemodialysis (HD) patients were taking at least one medication that contained phosphate. The median phosphate burden from prescribed medications was 111 mg/day [165]. Some of the multivitamin supplements contain significant amounts of phosphorus (e.g., one Centrum tablet contains 48-mg phosphorus), and it is important to be aware of this when designing a low-phosphorus diet for CKD patients [20]. Therefore care should be taken concerning the phosphate content of drug formulations when prescribing such medications.

Patient education regarding high-phosphorus foods is an important component of the management of hyperphosphatemia. To determine the effect of limiting the intake of phosphorus-containing food additives on serum phosphorus levels among patients with end-stage renal disease, Sullivan et al. assessed 279 patients with elevated baseline serum phosphorus levels greater than 5.5 mg/dL. The intervention group ($n = 145$) received counseling on avoiding foods with phosphorus additives. After 3 months, there was a 0.6 mg/dL decline in the average serum phosphorus level among the educated participants compared with control participants (95% CI, −1.0 mg/dL to −0.1 mg/dL). The authors found that counseling patients with ESRD to avoid phosphorus-containing food additives resulted in a modest but clinically significant improvement in serum phosphorus levels [178].

The Food and Drug Administration requires products to include a nutrition facts label that lists the content of several important nutrients, including calories, cholesterol, sodium, protein, and calcium. However, many nutrition labels fail to list the phosphorus content, making it difficult for patients to know how much phosphorus they are ingesting. In one study, Sullivan and colleagues found that phosphorus content was not listed on any of 38 representative chicken products purchased in grocery stores even though 92% of these products contained phosphorus additives [179].

Educating dialysis patients to limit their intake of additive-containing food products constitutes an important dietary recommendation. However, following such recommendations can be challenging for multiple reasons. The availability of additive-free products in grocery stores may be limited. Additive-free products are more expensive and require more effort to prepare, which may represent a serious limitation for dialysis patients with physical or social challenges. In addition, ingredient lists are generally not present on fast food items, making it difficult to identify phosphorus-containing additives. Simply knowing that a product contains a phosphorus additive does not allow an accurate estimate of its phosphorus content.

There is a need for labeling changes, and hopefully in the future the policymakers will mandate that phosphorus content of foods must be included on the nutrition facts label. This will encourage manufacturers to limit the use of phosphorus additives, will help patients limit their phosphorus intake, will guide providers to better instruct patients, and will help care providers and researchers to accurately assess dietary intake.

Dietary phosphorus, protein intake, and phosphorus–protein ratio

Foods rich in protein are an important source of dietary phosphorus. Thus dietary restriction of phosphorus is frequently associated with a decrease in dietary protein intake. This can lead to malnutrition and protein-energy wasting, important risk factors for death in maintenance dialysis patients [180]. A 3-year study of 30,075 prevalent maintenance hemodialysis patients showed that a decrease in serum phosphorus that was occurred with a concomitant decrease in protein intake increased the risk of death. The patients whose serum phosphorus decreased and whose normalized protein equivalent of total nitrogen appearance (nPNA) increased over 6 months had greater survival, with a case mix–adjusted death risk ratio of 0.90 (95% confidence limits: 0.86, 0.95; $P < .001$). In contrast, those whose serum phosphorus increased but whose nPNA decreased or those whose phosphorus and nPNA both decreased had worse mortality with risk ratio of 1.11 (1.05,1.17; $P < .001$) and 1.06 (1.01,1.12; $P = .02$), respectively. The authors concluded that the risk of controlling serum phosphorus by restricting dietary protein intake may outweigh the benefit of controlling phosphorus and may lead to greater mortality [181].

Noori et al. conducted a cohort study in 224 maintenance hemodialysis patients to examine the survival predictability of dietary phosphorus and the ratio of dietary phosphorus (in mg) to protein intake (in g). Both higher phosphorus intake and a greater dietary phosphorus to protein ratio were associated with increased death risk in hemodialysis patients, even after adjustments for serum phosphorus, type of phosphate binder used, and dietary protein, energy, and potassium intake [182]. The ratio of dietary phosphorus to protein may represent a better dietary phosphorus metric for CKD patients. The metric phosphorus to protein ratio is also recommended by the KDOQI guidelines.

There is a great variation in the ratio of phosphorus to protein among different protein sources. Low phosphorus-to-protein ratios are found in nondairy animal-derived foods, including egg whites, while whole eggs, dairy products, legumes, and fast foods have higher phosphorus-to-protein ratios. Egg whites are an excellent source of high-quality protein, with a low phosphorus-to-protein ratio and a low-cholesterol content. Taylor et al. conducted a pilot dietary intervention study in 13 hemodialysis patients who substituted pasteurized liquid egg whites for meat at one meal per day. Serum phosphorus level decreased significantly by 0.9 mg/dL over 6 weeks, while serum albumin level tended to increase. Pasteurized liquid egg white products were well tolerated and may become an important dietary protein source for CKD patients [183].

Sherman and his colleagues measured the phosphorus and protein content of 44 food products, including 30 refrigerated or frozen precooked meat, poultry, and fish items, using the Association of Analytical Communities official method. The authors found that the ratio of phosphorus to protein content ranged from 6.1 to 21.5 mg of phosphorus per 1 g of protein. The mean ratio was 14.6 mg/g in the 19 food products with a label listing phosphorus as an additive compared with 9.0 mg/g in the 11 items without listed phosphorus [184]. For example, whey protein has a low phosphorus-to-protein ratio, making it an excellent source of protein supplementation, without worsening of hyperphosphatemia [185].

In addition to the phosphate content of a food, measures targeting a decrease in phosphorus levels should also depend upon an understanding of the ability to absorb phosphorus within the gastrointestinal tract. In contrast to highly bioavailable phosphorus additives, plant-derived phosphorus is less well absorbed by humans. One of the few studies done on the absorbability and metabolic consequences of dietary phosphorus from different food sources involved 16 young Finnish females who were fed five experimental diets: a control diet that contained 500 mg of phosphorus, and four diets containing the same amounts of phosphorus (~1500 mg), but from different sources, such as meat, cheese, whole grains, or phosphate supplements. Each diet was consumed for 1 day, during which time serum levels of phosphate and 24-hour urinary phosphate excretion were measured. Based on serum phosphorus and urinary phosphate excretion, phosphorus contained in meat, cheese, and supplements appeared to absorb better than phosphorus from whole grains, suggesting lower intestinal absorption of phosphorus with the grain-based diet. Moe et al. conducted a crossover trial in nine patients with CKD stage 3 or 4 (estimated GFR 25–40 mL/min) and normal serum phosphorus to directly compare a grain-/soy (vegetarian)-based protein diet to a meat-/dairy (meat)-based protein diet with equivalent nutrients. The study demonstrated that 7 days of the vegetarian diet resulted in lower serum phosphorus levels, decreased FGF-23 levels, and a trend toward decreased 24-hour urinary phosphorus excretion [186].

In conclusion, renal patients should be educated on how to substitute protein sources with high phosphorus bioavailability, such as enhanced meats, processed cheese, or fast food, with sources that have low phosphorus bioavailability, such as whole-grain and unprocessed foods [187,188]. While changing the therapeutic approach to decrease the amount of foods that are high in phosphorus additives and/or that have a high phosphorus-to-protein ratio seems to help control the phosphorus, more human studies are needed to support the efficacy of these approaches.

Phosphate removal with dialysis

Phosphate is unevenly distributed throughout the body, being predominantly localized in the intracellular space. Hence, most phosphate removed during dialysis is derived from the intracellular space. The kinetics of phosphate removal differ significantly from classic urea kinetics. During the first phase of dialysis, there is a rapid decline in serum phosphate levels due to phosphate removal from the extracellular space. This is followed by a second phase during which phosphate removal continues but at a lower rate, but plasma phosphate level does not further decline, as a consequence of phosphate mobilization from a pool other than the extracellular fluid. The rate of change in plasma phosphate levels is most likely determined by the rate of phosphate transfer from one or more intracellular compartments to plasma compartment. A large rebound of phosphate occurs within a couple of hours after termination of dialysis, reaching about 80% of predialysis values [189–191].

Phosphate removal varies among the different modalities of dialysis. With conventional, thrice-weekly hemodialysis (4 hours), phosphate removal ranges from 600 to 900 mg per treatment (1800–2700 mg/week). Conventional hemodiafiltration improves phosphate removal (1170 mg per treatment), but overall, conventional, thrice-weekly intermittent hemodialysis is largely inadequate for the elimination of the total amount of phosphate absorbed from the intestinal tract in 1 week (4000–5000 mg) from a standard protein intake [192,193]. In short daily hemodialysis the amount of phosphate removal depends on session length and frequency of sessions. A study by Ayus et al. compared 51 patients treated with conventional hemodialysis (three sessions/week of 4 hours each) with 26 patients treated with short daily hemodialysis (six sessions/week of 3 hours each). There was a significant decrease in serum phosphate levels in patients on short daily hemodialysis from a baseline of 6.26 ± 2.57–4.58 ± 1.06 at 6 months ($P < .0001$) and 4.20 ± 1.16 at 12 months ($P < .0001$), compared with conventional thrice-weekly hemodialysis, where serum phosphate was 4.98 ± 1.49 at baseline and 5.02 ± 1.14 at 12 months. In 70% of patients in the short hemodialysis group phosphate binders were discontinued by the end of the study period. They also found that serum phosphate levels were independently associated with a reduction in left ventricular mass index, likely through increases in vascular compliance [194].

Phosphate is effectively removed with nocturnal hemodialysis. Mucsi et al. compared eight patients on conventional hemodialysis (three sessions per week of 4 hours each) with eight patients on nocturnal hemodialysis (six sessions per week of 8 hours each). The weekly phosphate removal was more than twice with nocturnal hemodialysis as compared to conventional hemodialysis, with significantly lower average serum phosphate levels in the nocturnal hemodialysis group (4 vs 6.5 mg/dL) [195]. Similar results were obtained in a study comparing patients undergoing conventional three-times weekly hemodialysis with hemodialysis sessions of extended duration that were adjusted to provide a similar eKT/V(urea), phosphate removal was 40% higher with extended hemodialysis as compared to conventional hemodialysis. Interesting, although hourly mass removal of phosphate was higher during conventional hemodialysis, the prolonged lower rate of phosphorus removal that was conducted for a longer period of time led to a higher phosphate removal in the extended hemodialysis period [196].

Another randomized trial involved 52 patients who were assigned to receive nocturnal hemodialysis six-times weekly or conventional hemodialysis three-times weekly. In the nocturnal hemodialysis group, the average predialysis serum phosphate levels were reduced from 5.5 ± 1.5 to 4.4 ± 1.7 mg/dL, and phosphate binders were reduced or discontinued in 73% of the patients [197]. Incenter, three-times weekly nocturnal hemodialysis has been shown to improve phosphate management. Bugeja et al. reported their results in 39 patients who were switched from three-times weekly conventional hemodialysis to three-times weekly incenter nocturnal hemodialysis. After conversion to incenter nocturnal hemodialysis, median phosphate levels decreased from 5.9 to 3.7 mg/dL, and the mean daily dosage of phosphate binders declined from 6.2 to 4.9 pills/day at study end [198]. Interestingly, in a recent study that analyzed phosphate removal during hemodialysis, it was observed that phosphate removed during the first hour corresponded to 25% of the total phosphate removed, and that most of the phosphate was removed during the rest of the procedure [199]. The authors suggested that in patients receiving more frequent nocturnal hemodialysis, lower phosphate levels are attained not because phosphate is removed during the first 1–2 hours of hemodialysis, but because it is performed more frequently.

In conclusion, hemodialysis removes phosphorus, but its typical regimen of three times per week, together with dietary phosphate restriction, is usually not enough to control serum phosphorus levels. Increasing the length and frequency of HD improves phosphate removal and may be enough to control hyperphosphatemia, but application of this type of regimen in a large scale may be impractical and too costly.

Many peritoneal and intrinsic factors influence phosphate transport and clearance during peritoneal dialysis. Weekly average phosphate removal in patients on continuous ambulatory peritoneal dialysis (CAPD) has been reported to be around 70 mmol (2170 mg) with 4 × 2 L exchanges per day and 105 mmol (3250 mg) with 4 × 3 L exchanges per day [200]. Peritoneal phosphate clearance is lower than the clearance of small water-soluble substances. Some studies show that peritoneal phosphate clearance correlates better with creatinine clearance than with urea removal [201,202]. In a retrospective study that involved 129 peritoneal dialysis patients, there was a strong correlation between peritoneal phosphate and creatinine clearance. In the multivariate regression analysis, peritoneal phosphate clearance was independently associated with peritoneal creatinine clearance and not with Kt/V urea. This suggests that peritoneal creatinine clearance can be used as a surrogate marker for peritoneal phosphate clearance [201].

Peritoneal phosphate clearance is influenced by the different peritoneal dialysis modalities and across different peritoneal membrane transport characteristics. For patients in the high transport category, no difference in phosphate clearance is observed between CAPD and continuous cyclic peritoneal dialysis (CCPD). For patients in the high average, low average, and low transport category, peritoneal phosphate clearance is higher with CAPD than with CCPD, whereas creatinine clearance does not differ. These results suggest that in high average, low average, and low transporters, peritoneal phosphate clearance may be increased by increasing cycler dwell times, and by increasing the number of exchanges for high transporter patients. All patients may benefit from increased convective peritoneal phosphate clearances through higher ultrafiltration rates. However, there are no available studies on the effect of increased ultrafiltration rates on peritoneal phosphate clearance [201,203].

In conclusion, weekly phosphate removal by the usual dialysis treatments is inadequate in comparison to the usual weekly dietary phosphate intake, and additional therapy may be required to maintain desirable serum phosphate levels. Many CKD patients and the majority of chronic dialysis patients require administration of oral phosphate binders to control serum phosphate.

Aluminum binders

Aluminum hydroxide, an effective phosphate binder, was the binder of choice for many years, but due to the gradual tissue accumulation of absorbed aluminum, long-term use of this binder was found to be associated with cognitive disturbances, osteomalacia, refractory microcytic anemia, and myopathy [204–208]. There is no evidence to suggest that even low levels of exposure to aluminum is safe for chronic use of this binder.

Calcium-based binders

Calcium acetate and calcium carbonate are inexpensive and effective in controlling hyperphosphatemia. However, there is increasing concern that they cause positive calcium balance, vascular calcification, and CVS mortality in patients with advanced CKD [18,132,209,210]. Calcium carbonate has poor solubility in a nonacid environment, which is required for optimal calcium phosphate binding, and many patients with severe renal failure have achlorhydria or are taking H2-blockers or proton pump inhibitors (PPIs). Calcium acetate, on the other hand, is more soluble at a higher pH. Several studies have found calcium acetate to be more effective than calcium carbonate at binding intestinal phosphate per mmol of administered elemental calcium. The clinical significance of this effect is unclear, with a few studies reporting equivalent rates of hypercalcemia [211–213]. Hypercalcemia is most likely to occur when these binders are used in combination with a vitamin D analog. Long-term use of calcium-based phosphate binders may contribute to soft tissue and vascular calcification. They can also result in oversuppression of PTH and the development of a dynamic bone disease [139,214,215]. As a consequence, noncalcium-based phosphate binders have been developed and are increasingly used to control phosphate absorption without causing a calcium burden. These agents include sevelamer, lanthanum carbonate, magnesium, and iron-based agents. However, controversy still exists regarding the effects of these binders on calcium balance, vascular calcification, and mortality as discussed in the next sections.

Sevelamer

Sevelamer hydrochloride and sevelamer carbonate are nonaluminum, noncalcium phosphate–binding polymers that bind phosphate through ion exchange. Since sevelamer carbonate does not decrease serum bicarbonate levels, it may be more appropriate for patients at risk for metabolic acidosis. The two agents appear to be equivalent in their ability to control serum phosphate levels. This was demonstrated in a double-blind, randomized study of 79 hemodialysis patients, who were randomly assigned to either sevelamer carbonate or sevelamer hydrochloride for 8 weeks, followed by a crossover to the other regimen for an additional 8 weeks of treatment. Sevelamer carbonate and sevelamer hydrochloride were equivalent in controlling serum phosphorus, while serum bicarbonate levels increased with sevelamer carbonate [216–218]. Many clinical studies have shown that sevelamer is effective in lowering serum phosphate levels and is generally well tolerated. Furthermore, sevelamer binds bile acids, decreases fecal bile acid excretion, and lowers Low Density Lipoprotein (LDL) cholesterol [216,219–221].

Several randomized clinical trials that compared sevelamer and calcium salts demonstrated similar phosphate-lowering abilities [151,222,223]. Unfortunately, the designs of these studies have been heterogeneous in patient selection, duration of follow-up, and outcome measures, making comparisons between studies difficult to interpret. In the prospective Treat-to-goal (TTG) Trial [152], 200 hemodialysis patients were assigned to receive sevelamer or a calcium-based phosphate binder. At 1 year, sevelamer and calcium-based binders provided equivalent control of serum phosphate levels (5.1 ± 1.2 vs 5.1 ± 1.4 mg/dL, respectively), but serum calcium concentrations were significantly higher in the calcium-treated group ($P = .002$). The use of sevelamer was also associated with a lower incidence of hypercalcemia (15% vs 16%) and a decreased incidence of low PTH levels (30% vs 57%). Other randomized clinical studies conducted to compare sevelamer to calcium-based binders showed beneficial effects of sevelamer on biochemical parameters, including C-reactive protein, LDL cholesterol, uric acid, fetuin-A, and FGF-23. Whether these potential treatment benefits with sevelamer lead to more favorable clinical outcomes is yet to be determined [80,224–226].

The results of the studies on progression of vascular calcification with sevelamer versus calcium-based phosphate binders have been contradictory. In the TTG trial, the median percentage change in CAC score from baseline was significantly greater with calcium-based binders than with sevelamer at both 26 weeks (14% vs 0%, $P = .002$) and 52 weeks (25% vs 6%, $P = .04$) [152]. The Renagel in New Dialysis (RIND) was a prospective, randomized study that compared the effect of sevelamer and calcium-based binders on the progression of vascular calcification in 129 incident hemodialysis patients. Subjects treated with calcium-based phosphate binders showed more rapid and more severe increases in CAC score when compared with those receiving sevelamer hydrochloride ($P = .056$ at 12 months, $P = .01$ at 18 months) [151]. By comparison the Calcium Acetate Renagel Evaluation 2 trial was a noninferiority trial designed to compare the effects of sevelamer and calcium-based phosphate binders on progression of coronary artery calcification in hemodialysis patients. After 12 months of therapy, no significant difference was observed in progression of the coronary artery calcification between these two groups. The study was limited by its short duration, substantial drop-out rates, and the inclusion of a higher proportion of diabetic patients [226]. The same effects of treatment on coronary artery calcification were found in the Phosphate Binder Impact on Bone Remodeling and Coronary Calcification study where 101 hemodialysis patients were assigned to sevelamer or calcium acetate. Due to the inconsistencies among these study results, larger studies will be needed to determine the effect of sevelamer on vascular calcification [226–228].

Studies comparing mortality with phosphate binders are controversial. A few studies evaluated mortality rates with sevelamer versus calcium-based phosphate binders. In a post hoc analysis of the RIND study, mortality rate at a median follow-up of 44 months was higher in calcium-treated patients (10.6/100 patient years, 95% CI 6.3–14.9) than in sevelamer-treated patients (5.3/100 patient years, 95% CI 2.2–8.5; $P = .05$). With multivariate analysis, there was a greater risk of death for patients treated with calcium-based phosphate binders (HR 3.1, CI 1.23–7.61; $P = .016$) [146]. The Dialysis Clinical Outcomes Revisited study enrolled 2103 hemodialysis patients who were assigned to treatment with either sevelamer hydrochloride or calcium (70% to calcium acetate and 30% to calcium carbonate) [223]. The primary analysis showed no significant difference in all cause and cause-specific mortality between the two groups (HR with sevelamer, 0.93; 95% CI, 0.79–1.10). However, there was a significant age interaction as only in the patients who were greater than 65 years old; there was an effect of sevelamer on lowering mortality rate. Criticisms of this study include a high rate of loss to follow-up, long-time undergoing dialysis treatment and high percentage of diabetics [229–231]. Several metaanalyses have addressed these aspects. In one of them the results of five randomized trials consisting of 2429 patients showed a similar risk difference for all-cause mortality between sevelamer hydrochloride and calcium-based agents (risk difference, −2%; 95% CI, −6–2) [232]. More recent metaanalysis of randomized trials comparing noncalcium versus calcium-based binders on mortality showed that patients treated with noncalcium binders had a 22% reduced mortality compared to those assigned to calcium-based phosphate binders [233]. In another metaanalysis of randomized controlled trials of patients with CKD stages 3–5 and patients on dialysis treated with calcium-based binders compared with sevelamer, patients treated with sevelamer had lower all-cause mortality, but no significant difference in CVS mortality was observed. In addition, in the group treated with sevelamer the risk of hypercalcemia was lower and PTH levels were higher. Serum phosphate levels were not significantly different between groups [229]. In most of the studies, combined gastrointestinal side effects occurred more often with sevelamer.

In conclusion, although controversy still exists about the possible benefits of sevelamer compared with calcium-based phosphate binders [234,235], the majority of randomized studies suggest that calcium-based binders and sevelamer are similarly effective at lowering phosphate. However, sevelamer is associated with less CVS or all-cause mortality and a lower risk of hypercalcemia and CAC. These aspects and the cholesterol-lowering effect of sevelamer should be considered when choosing a phosphate binder in patients with high CVS risk.

Lanthanum

Lanthanum carbonate is another phosphate binder able to bind phosphate across a wide pH range. Short-term trials demonstrate the efficacy of lanthanum carbonate in lowering serum phosphate levels, reducing iPTH, and potentially decreasing FGF-23 levels [236–239]. Clinical studies that compared lanthanum with other phosphate binders mainly evaluated their effects on biochemical parameters and on bone histology. Lanthanum and calcium-based phosphate binders appear to be similarly effective in reducing serum phosphate concentrations in patients with end-stage renal disease. In the largest trial the proportion of patients who had documented episodes of hypercalcemia was significantly smaller among the patients receiving lanthanum (4.3%) than among those receiving standard care, in the majority of cases, with calcium-based phosphate binders (8.4%) [240,241].

There has been concern about the possibility of lanthanum given the past experience with aluminum-based phosphate binders [242]. However, the pharmacodynamics of lanthanum are differs than that of aluminum, and there has not been demonstrated the accumulation of lanthanum in the CNS. With respect to bone, in a study of patient receiving lanthanum carbonate compared to standard therapy for over 2 years, phosphate control was similar in the two groups, but those receiving lanthanum carbonate showed higher bone turnover after 1 year and higher bone volume after 2 years with lanthanum carbonate [243].

Comparative studies of lanthanum carbonate and calcium-based binders with sevelamer are limited. In a preliminary study of chronic dialysis patients followed for 3 years, lanthanum carbonate and calcium carbonate yielded similar results in terms of effectiveness as phosphate binders, and no statistically significant differences were observed in terms of CVS mortality [244]. Similarly, there were no statistically significant difference in serum PTH levels between the two groups. Side effects of lanthanum carbonate are particularly gastrointestinal. Thus patients may find the lanthanum carbonate pills difficult to swallow, as the tablets require crushing or breaking into smaller pieces.

Newer phosphate binders

In recent years, newer phosphate binders have entered the market for use in chronic dialysis patients. These include, iron-based products, and magnesium salts. Ferric citrate and sucroferric oxyhydroxide bind phosphate in the intestine and reduce serum phosphate levels. A randomized study comparing ferric citrate with sevelamer and calcium-based binders shows effective serum phosphate control. Calcium and PTH levels were not different between groups. In addition, ferric citrate increased iron stores and decreased requirements for intravenous iron and erythropoietin-stimulating agents while maintaining hemoglobin levels [245,246]. Based on these properties, ferric citrate is also approved as an iron replacement product for the treatment of iron deficiency anemia in adult CKD patients not treated with dialysis [247]. However, gastrointestinal effects and pill burden are frequent limitations of ferric citrate while sucroferric oxyhydroxide requires chewing or crushing before ingestion.

In conclusion, the evidence available favors a benefit of controlling serum phosphate levels in CKD, particularly in advanced CKD. All phosphate binders currently in use are similarly effective at reducing serum phosphate levels. Nevertheless, hyperphosphatemia continues to be a frequent problem in CKD patients. In addition, phosphate binders are not devoid of side effects that in many cases limit their use. Ideally, the choice of the binder should be based on its capacity to adequately control serum phosphate levels while minimizing side effects, and particularly vascular calcification. In many cases, single approaches are not sufficient to maintain phosphate levels within the normal range. As suggested by KDIGO guidelines [2], phosphate-lowering measures should be used in concert to control hyperphosphatemia in a patient-oriented approach. These measures include diet, phosphate binders, and adequate dialysis. In addition, as will be discussed in the next sections, in patients with SHPT, reduction of PTH levels is important as PTH actions on bone results in bone resorption and release of phosphate which, in turn, increases serum phosphate levels independent of intestinal absorption.

Noncalcium binders should be the preferred binders due to the data associating calcium-based binders with CVS and all-cause mortality, and vascular calcification, particularly in those patients at higher risk of vascular calcification. In this regard the KDIGO guidelines suggest restricting the dose of calcium-based phosphate binders in patients with CKD G3a-G5D receiving phosphate-lowering treatment (2B). However, noncalcium binders are more expensive, an important concern in health-care systems that have lower insurance coverage. Gastrointestinal side effects and a higher pill burden are more frequent with noncalcium binders. Finally, the effects of phosphate binders on clinical outcomes remain controversial. Thus more placebo-controlled studies are necessary to more definitively examine whether the reduction of serum phosphorus by phosphate binders improves clinical outcomes.

Therapy with vitamin D sterols

Because the decrease in calcitriol production plays an important role in the development and maintenance of SHPT, the use of vitamin D sterols represents an important part of the treatment of hyperparathyroidism in CKD patients. Vitamin D sterols suppress PTH secretion, increase the absorption of both calcium and phosphorus from the gut, and appear to be associated with a survival advantage in chronic hemodialysis and CKD patients [248–250]. There are six active vitamin D derivatives currently available: calcitriol, alfacalcidol, doxercalciferol, 22-oxacalcitriol, falecalcitriol, and paricalcitol. In the United States the available agents include calcitriol, paricalcitol, and doxercalciferol.

Calcitriol is the natural form of active vitamin D produced by the human body and was the first vitamin D agent used for the treatment of hyperparathyroidism. Early studies with calcitriol in experimental animals as well as in clinical studies suggested that intermittent intravenous calcitriol was more effective and better tolerated than oral calcitriol. This was thought to be due to greater delivery of the vitamin D metabolite to peripheral target tissues other than the intestine [251]. Subsequent studies have shown that both intermittent oral and intravenous bolus therapy were equally effective with regard to PTH suppression and the side effects of treatment [252].

The vitamin D analog, paricalcitol, was introduced and developed to obtain a more selective suppressive action on the parathyroid gland while minimizing the propensity of vitamin D sterols to cause hypercalcemia and hyperphosphatemia. In experimental animals, paricalcitol was effective in suppressing PTH while inducing less hypercalcemia and hyperphosphatemia than calcitriol [253]. However, direct head-to-head randomized studies in patients are limited. A double-blind, randomized, multicenter study compared the safety and effectiveness of intravenous paricalcitol and calcitriol in suppressing serum PTH concentrations among 263 hemodialysis patients. The primary end point was greater than 50% reduction in baseline PTH, and the secondary end points were the occurrence of hypercalcemia and an elevated serum CaxP product. Paricalcitol treatment reduced PTH concentrations more rapidly with fewer sustained episodes of hypercalcemia or an increased CaxP product than calcitriol therapy [254].

Doxercalciferol, a prohormone that is hepatically activated into a VDR agonist, has similar efficacy compared to paricalcitol, albeit larger doses are required for PTH suppression. Studies with oral and intravenous formulations of doxercalciferol showed that both preparations are well tolerated and able to lower plasma PTH, with less frequent hypercalcemia seen with intravenous treatment [255].

Although the effectiveness of active vitamin D analogs in controlling SHPT has been demonstrated in multiple studies, particularly with regard to biochemical endpoints in patients with CKD 3–5 and in ESRD patients on dialysis [254,256], relatively few studies have examined their effect on bone histomorphometry [257,258]. Therefore more studies are required to evaluate the effect of these agents on bone and other organs. In this regard, KDIGO guidelines suggest that in adult patients with CKD G3a–G5 not on dialysis calcitriol and vitamin D analogs not be routinely used (2C), and that it is reasonable to reserve the use of calcitriol and vitamin D analogs for patients with CKD G4–G5 with severe and progressive hyperparathyroidism (not graded). However, it has been claimed that there is ambiguity in this guideline because the term "severe" is not defined [259]. In patients with CKD 5D, KDIGO guidelines suggest PTH-lowering therapy with calcitriol or vitamin D analogs (2B) [2]. Hypercalcemia and excessive suppression of PTH are the main concerns with this type of therapy.

Another limitation of active vitamin D analogs is their limited capacity to reduce serum PTH levels to appropriate values, particularly in patients with severe SHPT with nodular hypertrophy in whom VDR expression in the parathyroid cells are decreased or downregulated. In these cases the use of other agents alone or in combination with vitamin D analogs may be required.

Low serum levels of 25(OH) vitamin D are a frequent finding in CKD patients. Since 25(OH) vitamin D is the substrate for calcitriol, it seems logical to correct vitamin D deficiency or insufficiency by providing cholecalciferol or ergocalciferol, the natural forms of vitamin D, as a mean to increase calcitriol levels. However, suppression of PTH secretion with native vitamin D to control SHPT may not be sufficient, and the use of active vitamin D analogs or other PTH lowering agents is often required. Nevertheless, native vitamin D continues to be used in CKD patients because other actions in addition to the treatment of SHPT may be beneficial to the patient [82].

Studies have shown that calcifediol, a vitamin D prohormone, is safe and effective for treating SHPT and vitamin D insufficiency in patients with CKD stage 3 or 4 [260]. More studies are needed to examine in more detail the effects of calcifediol on end organs.

Calcimimetics

The CaSR in the parathyroid gland plays a central role in the management of SHPT. This receptor, highly sensitive to changes in calcium concentrations, also responds to other substances known as calcimimetics that can act allosterically as modulators of PTH secretion. Natural calcimimetics, such as magnesium and other inorganic compounds, act directly at the CaSR in the parathyroid gland and decrease PTH secretion (calcimimetics type l). Calcimimetics type ll [261] bind to a site different from the physiological ligand, increasing the sensitivity of the CaSR, which results in the inhibition of PTH secretion at lower calcium concentrations [261,262]. Several prospective randomized studies in chronic dialysis patients with hyperparathyroidism have found that the calcimimetics produce a dose-dependent reduction in the plasma PTH concentrations and a decrease in the serum calcium and phosphate levels [263–266]. Cinacalcet, a compound used daily and orally, is the calcimimetic most extensively used for the treatment of SHPT [96,262–264]. More recently, etecalcetide, a new generation of calcimimetics, is increasingly used [267]. This compound is used intravenously and due to its longer metabolism, it is administered three times a week during dialysis. Several randomized controlled trials have demonstrated the efficacy of these compounds at decreasing PTH levels [268,269]. Calcimimetics also decrease serum calcium and phosphorus levels [267–270]. The effectiveness of cinacalcet has been demonstrated in patients who did not achieve adequate PTH control because of their elevated serum calcium and phosphate levels while they received therapy with active vitamin analogs [263]. In contrast to cinacalcet, etelcalcetide may activate the CaSR even in the presence of hypocalcemia, and its longer half-life confers the advantage that it can be administered only three times a week at the end of a hemodialysis session. In patients on hemodialysis with moderate-to-severe SHPT who were randomized to etelcalcetide or cinacalcet for 26 weeks, patients given etelcalcetide were more likely to attain a reduction of PTH greater than 30% compared to the cinacalcet group [268]. Etelcalcetide also demonstrated noninferiority compared with cinacalcet and, in fact, was superior at achieving control of serum PTH levels. More patients in the etelcaletide group achieved more than 50% reduction in PTH levels compared to patients in the cinacalcet group. The number of patients receiving calcium-based phosphate binders or higher calcium concentration in the dialysate increased in both groups, and side effects were not different.

Prospective randomized studies have shown that cinacalcet diminishes bone fractures [271]. Studies of bone histology also show that treatment with cinacalcet, in addition to decreasing serum PTH levels, improves bone histological parameters of hyperparathyroidism, particularly bone turnover and fibrosis, indicating improvement in parathyroid-associated bone disease. Adynamic bone disease, frequently associated with PTH over suppression, was observed in a few patients treated with cinacalcet [272–274]. In one study, one patient, who had overt hypophosphatemia at baseline that reoccurred during follow-up, developed osteomalacia. This patient also had PTH oversuppression while taking cinacalcet [272]. These studies demonstrate an end-organ effect of cinacalcet in controlling the bone disorders in SHPT. However, close follow-up is required of patients treated with cinacalcet or etelcalcetide, particularly with regard to the magnitude of changes in their serum PTH, because oversuppression of PTH may lead to low bone turnover disease.

The ADVANCE trial was a prospective, randomized, controlled trial designed to evaluate the effects of cinacalcet plus low-dose vitamin D on vascular and cardiac valve calcification in 360 prevalent adult hemodialysis patients. The results of the study showed that coronary artery calcifications and valvular calcifications were significantly lower in the cinacalcet plus low-dose vitamin D group than the vitamin D sterol alone group [275].

One of the most common side effects seen with calcimimetics is hypocalcemia, thought to occur after decreased mobilization of calcium from bone caused by reduced PTH levels. This can be managed by adjustments in calcium-based phosphate binders, reductions in cinacalcet dose, or using these maneuvers combined with low doses of vitamin D sterols in patients with moderate-to-severe hyperparathyroidism [276].

Some of the main concerns regarding the treatment of SHPT with PTH-lowering agents relate to the desired magnitude of reduction of serum PTH levels, when to start and when to stop treatment with PTH-lowering agents, and what agent or combination of treatments should be employed. One major limitation of treatment guidelines is that at present, the histomorphometric analysis of the bone continues to be “gold standard” for an effective diagnosis of the bone alterations in CKD. However, on clinical grounds, this application is very limited because it is invasive, requires expert analysis of the bone histology, is costly, and is difficult to apply on a large scale.

Several studies have attempted to establish a relationship between the type of bone disease and serum biochemical markers. The KDIGO and KDOQI workgroups and other organizations suggest ranges of serum PTH levels to be achieved in CKD patients. KDOQI guidelines suggest a serum PTH range of 150–300 ng/mL as the optimal limit to avoid low or high turnover [277]. Similarly, since PTH levels may vary with different assays used in clinical laboratories (see earlier), the KDIGO guidelines in 2009 suggested a serum PTH range between two and nine times the highest normal value for the PTH assay used, but very few studies have addressed this issue directly [1]. Because bone turnover is mainly a function of the degree of hyperparathyroidism, serum PTH levels have been used as a surrogate indicator of bone turnover. Intact PTH (iPTH) has been studied for the diagnosis of bone turnover in dialysis patients and, together with serum calcium, phosphorus, and total alkaline phosphatases or bone-specific alkaline phosphatase, is frequently used to guide the pharmacologic treatment of CKD-MBD.

Other bone biomarkers have been evaluated for their predictive value in assessing renal osteodystrophy, but results have been inconclusive. Furthermore, some studies have shown that in a high proportion of dialysis patients, bone turnover cannot be accurately predicted from serum PTH levels [278]. A cross-sectional retrospective study of 492 chronic dialysis patients from four different countries examined the accuracy of biochemical markers to predict bone histopathology. Serum PTH and alkaline phosphatase allowed the discrimination of low bone turnover from nonlow bone turnover, and high from nonhigh bone turnover [260]. The combination of these two markers offered a minimal additional degree of discrimination. The best PTH cutoff to discriminate low from nonlow bone turnover, bone formation rate per unit bone surface, (BFR/BS) was 103.8 pg/mL, whereas the best serum PTH cutoff to discriminate high from nonhigh bone turnover was 323.0 pg/mL. Similarly, the best cutoff for bone-specific alkaline phosphatase was 33.1 U/L for low from nonlow turnover, and 42.1 U/L for high bone turnover. These results indicate that serum iPTH, with some certainty, can be used to discriminate low bone turnover from high bone turnover, and these PTH values are consistent with the recommendations of both, KDOQI and KDIGO. These results also provide reasonable help regarding the questions of when to start and when to stop treating high bone turnover disease in dialysis patients. Therefore at present serum PTH, although with limitations, continues to be the most accurate discriminator between high and low bone turnover disease in patients in dialysis. However, it should be taking into account that bone turnover is not the only marker of bone disease in CKD and that markers for other known bone alterations in renal osteodystrophy have not been evaluated.

Parathyroidectomy

The availability of effective PTH-lowering agents has made parathyroidectomy less necessary. However, this is still an alternative method for some patients, especially those with severe SHPT with nodular hyperplasia, difficult to control by medical means [2]. Parathyroidectomy may be indicated in these latter patients who become hypercalcemic or hyperphosphatemic, which precludes treatment with active vitamin D analogs, or in patients in whom calcimimetics cannot control very high levels of serum PTH. Parathyroidectomy should also be considered in patients with severe SHPT and metastatic calcification or calciphylaxis.

Total parathyroidectomy with autotransplantation of parathyroid tissue in the forearm or subtotal parathyroidectomy is the procedure most frequently utilized. In a study performed in 1992, excellent results were reported with both procedures; however, satisfactory long-term control of parathyroid gland function was achieved in only one-third of the patients; the other two-thirds remained either hypoparathyroid or developing recurrent hyperparathyroidism [279]. Hypoparathyroidism after renal transplantation may be associated with hypercalciuria with nephrocalcinosis and renal failure.

Other complications of parathyroidectomy include recurrent laryngeal nerve palsy, persistent hyperparathyroidism, hypoparathyroidism, and hungry bone syndrome. Nevertheless, parathyroidectomy is a relatively safe procedure. In a recent study from a national database in the Netherlands of patients with ESRD-related hyperparathyroidism who underwent parathyroidectomy and kidney transplantation between 1994 and 2015, 13 patients (7.0%) required reexploration for persistent or recurrent disease, and 30-day mortality and complication rates were 0.0% and 7.9%, respectively [280]. When hyperparathyroidism recurs in dialysis patients, medicinal treatment to lower serum PTH can often be used, depending on the level of PTH. In some patients treated with total parathyroidectomy with the implantation of parathyroid tissue in the forearm, further surgery may be necessary to remove excess parathyroid tissue, or to explore for additional parathyroid glands in the neck. Conversely, hypoparathyroidism with hypocalcemia, which persists despite treatment with large doses of vitamin D and calcium, can be treated with recombinant PTH (teriparatide).

Conclusion

Disorders of bone and mineral metabolism begin early in the course of declining renal function and progress steadily as kidney function deteriorates. Numerous studies have shown a close relationship between SHPT and poor clinical outcomes. These include bone fracture, CVS morbidity and mortality, as well as all-cause mortality. Although studies demonstrating a causal relationship between disordered bone and mineral metabolism in CKD and clinical outcomes are still limited, knowledge of the pathophysiology of these alterations has led to important therapeutic strategies to correct the abnormalities. Indeed, CKD-associated mineral bone disease is complex and requires combined therapies for its management and prevention. These treatments include the regulation of phosphate and calcium metabolism, and agents that control serum PTH levels directly. In the majority of cases, combined therapy and individualization of approaches are recommended to attain optimal results.

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C H A P T E R

24

Phosphorus metabolism and fibroblast growth factor 23 in chronic kidney disease

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The kidneys play an integral role in bone and mineral metabolism. Serum phosphate concentrations are tightly regulated in healthy individuals through several mechanisms including dietary absorption, bone flux, and renal excretion. Reduced kidney function due to various pathological etiologies leads to compensatory adaptations to maintain normal serum phosphate. Fibroblast growth factor 23 (FGF23) is a bone-derived endocrine hormone that has emerged as a key phosphaturic hormone responsible for regulating serum phosphate.

Phosphate metabolism in health

The term phosphorus is used interchangeably with phosphate when referring to dietary composition and distribution in the body. However, since phosphorus occurs almost exclusively in anionic form in the body, the term phosphate will be used throughout this chapter.

About 85% of total phosphate is deposited in bone and ~10% in soft tissues, the remaining 2%−3% is found in serum [1]. At a pH of 7.4 the predominant phosphate species are HPO_4^{2-} and $H_2PO_4^{-}$, and changes in systemic or local pH can modify transmembrane phosphate transport [2]. Serum phosphate levels in adults are maintained in a narrow range of 2.4−4.5 mg/dL via tight regulation of the freely exchangeable pool. Deviations from this normal range—both low phosphate levels, that is, hypophosphatemia, and high phosphate levels, that is, hyperphosphatemia—can lead to altered cellular and organ function manifesting as bone disorders, anemia, tissue calcification, nephrolithiasis, and increased cardiovascular (CV) mortality. Serum phosphate levels, both in healthy individuals and those with chronic kidney disease (CKD), have a circadian rhythm with a morning nadir and late nocturnal peak [3,4].

Phosphate homeostasis is the physiological process of regulating net phosphate balance. Net phosphate balance refers to the difference between intestinal absorption of phosphate, shift of intracellular phosphate between extracellular and bone storage pools, and urinary and fecal losses. The net urinary losses are determined by reabsorption of phosphate from the glomerular filtrate (60%−80% of filtered phosphate) [1]. Phosphate flux between body compartments is summarized in Fig. 24.1. Dietary phosphate is absorbed in the small intestine predominantly by paracellular diffusion via intercellular tight junctions and to a lesser extent by active transport across the cells. Both intestinal active transport and renal reabsorption in the proximal tubule are mediated by sodium-dependent phosphate cotransporters (NaPi) belonging to the SLC20 and SLC34 gene families. Intestinal NaPi2b transporters are upregulated in response to the active form of vitamin D; that is, 1,25-dihydroxyvitamin D (1,25-VitD) leading to an increase in phosphate absorption [6]. In health, urinary phosphate losses are regulated by highly efficient, constitutively active phosphate reabsorption in the proximal tubules which is mediated by NaPi2a and NaPi2c cotransporters. These channels are regulated predominantly by parathyroid hormone (PTH) and FGF23.

Phosphate metabolism in chronic kidney disease

One of the earliest abnormalities to occur when kidney function decreases is a sustained reduction in tubular phosphate reabsorption [7]. This has been

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shown by demonstrating that as estimated glomerular filtration rate (eGFR) declines, total urine phosphate excretion decreases and fractional excretion of phosphate increases [8]. This is primarily a result of the increase in FGF23 and PTH via their effect of downregulating NPT2a and NPT2c transporters in the proximal tubule. Despite these compensatory changes in the levels of these phosphate-regulating hormones, serum phosphate remains within the accepted normal range until eGFR decreases to less than 20–30 mL/min/1.73 m^2; that is, hyperphosphatemia is usually not seen in patients with CKD stage 1–3 [9,10]. The change in phosphate, calcitriol, PTH, and FGF23 with worsening predialysis CKD is summarized in Fig. 24.2.

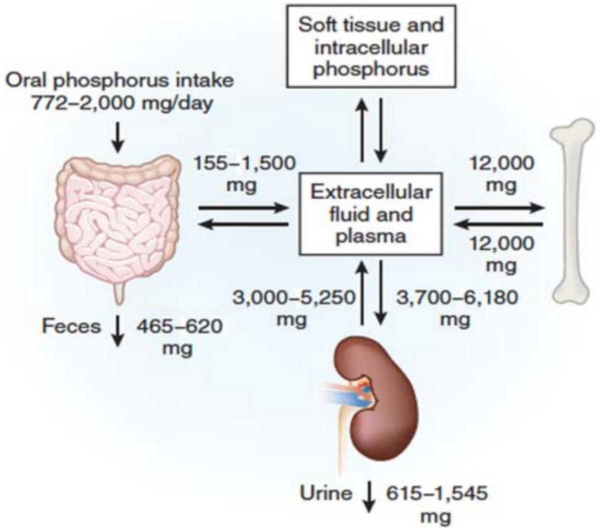
Soft tissue and intracellular phosphorus
Oral phosphorus intake 772–2,000 mg/day
155–1,500 mg
Extracellular fluid and plasma
12,000 mg
12,000 mg
3,000–5,250 mg
3,700–6,180 mg
Feces
465–620 mg
Urine
615–1,545 mg

FIGURE 24.1 Phosphate flux between body compartments [5]. *Source: Reprinted with permission from Blaine J, et al. Renal control of calcium, phosphate, and magnesium homeostasis. Clin J Am Soc Nephrol 2015;10(7):1257–72.*

FGF23's structure, synthesis, and function

The discovery that mutations in the gene encoding FGF23 cause autosomal dominant hypophosphatemic rickets led to a paradigm shift in our understanding of

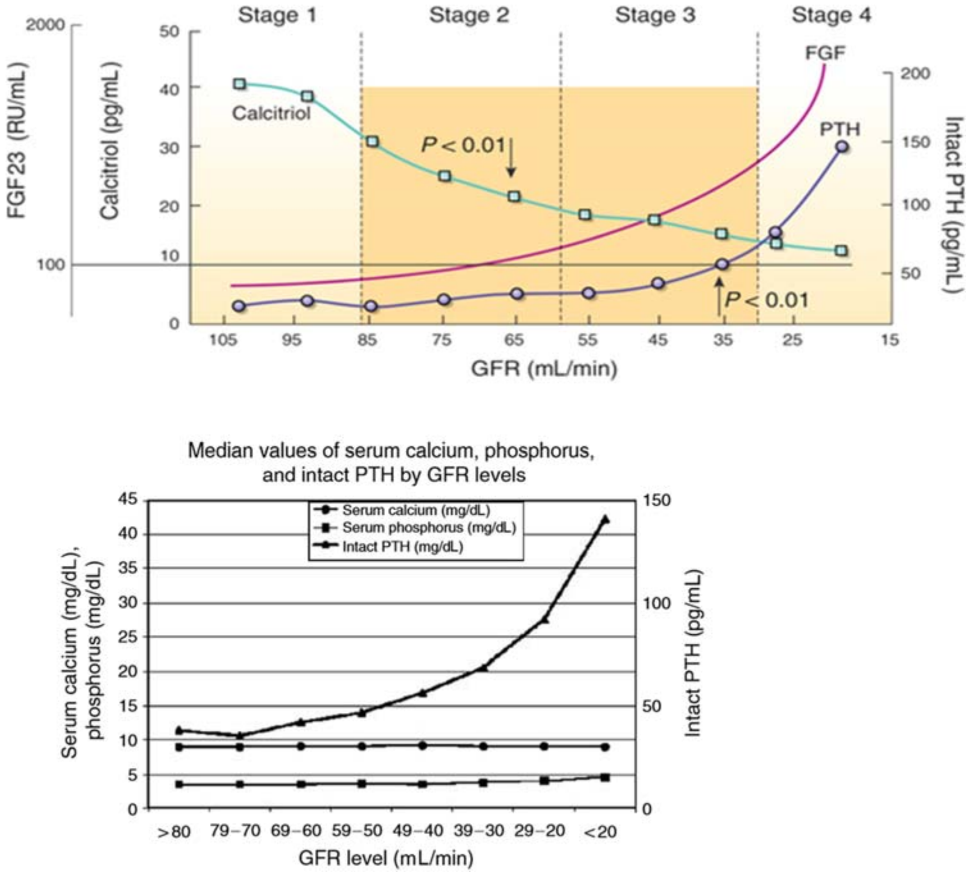

FIGURE 24.2 Changes in phosphate, calcitriol, PTH, and FGF23 with worsening CKD (this will be a combined figure using the figures below with the graph for phosphorus from the second figure superimposed on the first figure) [9]. *CKD*, Chronic kidney disease; *FGF23*, fibroblast growth factor 23; *PTH*, parathyroid hormone. *Source: Adapted from Levin A, et al. Prevalence of abnormal serum vitamin D, PTH, calcium, and phosphorus in patients with chronic kidney disease: results of the study to evaluate early kidney disease. Kidney Int 2007;71(1):31–8.*

the role of FGF23 in normal mineral metabolism [11]. FGF23 has since been shown to be central to the pathogenesis of other rare disorders of phosphate homeostasis including X-linked hypophosphatemia, autosomal recessive hypophosphatemic rickets, fibrous dysplasia, and tumor-induced osteomalacia [12]. These disorders are characterized by kidney phosphate wasting leading to hypophosphatemia, severe rickets or osteomalacia, inappropriately low serum 1,25D levels, growth retardation, and skeletal deformities.

The main sources of FGF23 are skeletal osteocytes, osteoblasts, and bone marrow stromal cells in the skeleton. FGF23 belongs to the FGF19 subfamily of endocrine FGFs and differs from other autocrine FGFs due to its unique C-terminal structure as well as a specific three-dimensional configuration with a lack of a heparin-binding domain that allows it to be secreted systemically [13,14].

The FGF23 gene is located on chromosome 12p13 in humans and encodes FGF23, which is a 32-kDa glycoprotein composed of 251 amino acids. It consists of a hydrophobic signal sequence (24 amino acids), an N-terminal FGF core homology domain (155 amino acids), and a C-terminal domain unique to FGF23 (72 amino acids) [13]. Wild-type FGF23 expression leads to the secretion of both intact FGF23 and cleaved N- and C-terminal peptide fragments.

FGF23 acts on target organs via binding to heterodimeric complexes of FGF receptors (FGFRs) and membrane-bound α-klotho (klotho) coreceptors that are expressed mainly in the kidney, parathyroid gland, and bone [15]. The N-terminal domain binds to the FGFR, while the C-terminal domain binds to the klotho. Four FGFRs exist and only FGFR1c requires klotho as a coreceptor to bind to FGF23. FGF23 can also exert effects in tissues that express FGFR2 and FGFR4, for example, myocardial tissue, hepatocytes, and neutrophils [16,17]. Binding of FGF23 to its receptor initiates signal transduction through activation of cytoplasmic tyrosine kinases that induce activation of signaling pathways, especially the FGFR substrate 2 (FRS2)−mitogen-activated protein kinase pathway and the phospholipase Cγ1 (PLCγ1)−calcineurin−nuclear factor of activated T cells (NFAT) pathway [18]. The obligate role of klotho was demonstrated by showing identical phenotypes result in knockout mice lacking FGF23 (FGF23 −/− mice) and Klotho (Klotho −/− mice) [19]. Soluble klotho, cleaved from the membrane-bound protein, may act as a portable receptor for FGF23.

There are two commercial ELISA assays to measure FGF23, an intact (i) and a C-terminus (c). Since the source of C-terminus FGF23 fragments is FGF23 transcription and subsequent peptide cleavage, high cFGF23 indicates increased transcription of FGF23 with the iFGF23-to-cFGF23 ratio reflecting the relative amount of cleaved FGF23. Combining cFGF23 results with simultaneous measurement of iFGF23 and serum phosphate can serve as a "liquid" bone biopsy for the assessment of FGF23 dynamics and differentiation of the FGF23 mediated syndromes [20].

FGF23 exerts its effects on the kidney by downregulating NaPi2a and NaPi2c transporters in the proximal tubule [21] leading to increased renal phosphate excretion in response to increased phosphate intake. It is the primary regulator of renal phosphate reabsorption by this mechanism. FGF23 causes decreased production of 1,25-VitD by decreasing conversion of 25-vitamin D to the activated form by inhibiting CYP27B1 (1α-hydroxylase) and increasing 1,25-VitD inactivation by stimulating CYP24A1 (24-hydroxylase) [21]. This decrease in 1,25-VitD leads to decreased intestinal absorption of calcium and phosphate from dietary sources. The effects of dietary phosphate loading on circulating FGF23 occur independently of changes in serum phosphate.

FGF23 production is stimulated by 1,25-VitD by its binding to the FGF23 promoter region which leads to an endogenous control of 1,25-VitD production via a negative feedback loop [22]. PTH on the other hand stimulates FGF23 directly, while FGF23 inhibits PTH via direct binding to FGFR1c in the parathyroid gland. The decrease in PTH indirectly leads to a further reduction in 1,25-VitD production [23] and decreased release of phosphate from bone.

FGF23 in chronic kidney disease

Across the entire spectrum of CKD, cross-sectional studies have shown that serum FGF23 levels increase with advancing stages of CKD. This rise in circulating FGF23 levels and the reduction in serum calcitriol levels precede the development of hyperphosphatemia [24,25]. In fact, the rise in FGF23 is seen in very early CKD in outpatients with stable CV disease (CVD) [26]. In rats with antiglomerular basement membrane nephritis and CKD stage 2−4, only serum FGF23 and creatinine were significantly elevated 10 days after the onset of CKD; serum PTH levels increased and 1,25-VitD levels decreased only after day 20. This study established that the mechanism of 1,25-VitD deficiency in CKD is a primary excess of FGF23 rather than decreased production due to loss of renal mass [27]. It was hypothesized that increased FGF23 secretion was critical for maintaining normal phosphate balance in early CKD, but with the trade-off of progressive 1,25-VitD deficiency due to elevated FGF23 levels [28]. The current thinking of the pathogenesis of CKD-associated mineral and bone disorders (CKD-MBDs) is summarized in Fig. 24.3 with FGF23 playing a central role.

The mechanism of how kidney disease modulates increased production of FGF23 from bone has been unclear. A recent study that used sampling of multiple

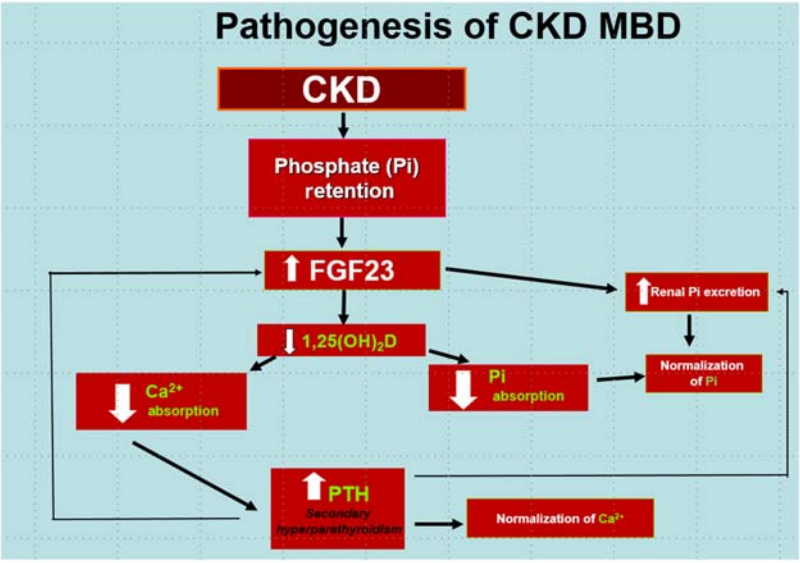

FIGURE 24.3 Pathogenesis of CKD-MBD. *CKD*, Chronic kidney disease; *MBD*, mineral and bone disorder.

proteins and metabolites in aortic and renal venous samples from human subjects with a mean eGFR of 66.6 mL/min/1.73 m^2 showed that renal vein glycerol-3-phosphate (G-3-P) had the strongest correlation with circulating FGF23. In mice, exogenous G-3-P stimulated bone and bone marrow FGF23 production through local G-3-P acyltransferase (GPAT)−mediated lysophosphatidic acid (LPA) synthesis. Further, the stimulatory effect of G-3-P and LPA on FGF23 required LPA receptor 1. In humans and mice with AKI (which increases FGF23 levels), there was a rapid increase in circulating G-3-P; and the effect of AKI on FGF23 was abrogated by GPAT inhibition or Lpar1 deletion [29].

Healthy individuals tend to have a higher circulating fraction of FGF23 fragments compared to patients with advanced kidney disease, where almost all the circulating FGF23 is iFGF23 [20,30].

CKD is commonly associated with functional iron deficiency and inflammation. In wild-type mice, chronic inflammation and chronic iron deficiency increased cFGF23 but only modestly increased iFGF23. Acute inflammation dramatically increased iFGF23 levels to a much greater extent in a mouse model of CKD versus wild-type mice suggesting that downregulated or impaired FGF23 cleavage may contribute to elevated iFGF23 in CKD [31]. However, the use of antiinflammatory therapies has not shown a significant effect of FGF23 reduction [32].

Role of phosphate and FGF23 excess

Role of phosphate excess in people without chronic kidney disease

Epidemiological studies in populations without CKD have shown an association of elevated serum phosphate with all-cause mortality [33,34], CVD [35], and CV mortality [36]. In a cohort of middle-aged women, a higher intake of phosphate was associated with an increased risk of type 2 diabetes [37]. In the Third National Health and Nutrition Examination Survey (NHANES), high dietary phosphate was associated with increased all-cause mortality [38]. Further, in this latter cohort, elevated fasting serum phosphate concentrations were associated with increased mortality, whereas higher nonfasting serum phosphate was not. This may be explained by reduced variability associated with measuring fasting levels [39]. In participants in the multiethnic study of atherosclerosis a cohort free of CVD, higher dietary phosphate intake was associated with increased left ventricular mass in men but not in women [40].

Serum phosphate levels in the high normal range have been associated with incident CKD and end-stage kidney disease (ESKD) in the general population, suggesting it a risk factor for kidney disease [41,42]. While these epidemiological studies suggest an association of serum phosphate with adverse outcomes, no study has shown the benefit of reducing serum phosphate in the general population on clinical outcomes.

Role of phosphate excess in people with chronic kidney disease

In an observational study in nondialyzed patients with CKD, elevated serum phosphate levels >3.5 mg/dL were associated with a linear increased risk for mortality, independent of renal function, and other known confounding factors [43]. Similar findings of an association between all-cause and CV mortality with increasing serum phosphate in patients with

CKD stage 3–4 were seen in a British cohort [44]. In a large cohort of prevalent maintenance hemodialysis (MHD) patients, hyperphosphatemia and secondary hyperparathyroidism (SHPT) were significantly associated with mortality and with all-cause, CV, and fracture-related hospitalization [45]. On the other hand, in the Modification of Diet in Renal Disease (MDRD) study, phosphate intake was not tightly linked with serum phosphate concentrations in CKD stage 3–5, and there was no evidence that greater phosphate intake, assessed by 24-hour phosphate excretion, was associated with ESKD, CVD, non-CVD, or all-cause mortality [46].

Role of FGF23 in people without chronic kidney disease

In the prospective Cardiovascular Health Study (CHS) involving community living individuals >65 years age, high serum cFGF23 levels were associated with all-cause mortality and incident heart failure. This was also observed in people without CKD, although the associations were particularly strong among persons with CKD [47]. In this same cohort, higher FGF23 levels were associated with increased prevalent frailty [48], increased incidence of first infection-related hospitalizations [49], greater left ventricular mass and left ventricular hypertrophy (LVH) [50], and greater risk of nonsudden cardiac death [51], but higher serum FGF23 was not associated with incident peripheral arterial disease [52] or hip fracture risk [53].

In the MESA (Multiethnic Study of Atherosclerosis) study in community-dwelling adults without CKD or CVD, high serum iFGF23 was associated with increased incident atrial fibrillation [54] and increased heart failure with preserved ejection fraction, but it was not associated with increased heart failure with reduced ejection fraction [55] or measures of arterial stiffness [56]. In the Framingham study cohort, high cFGF23 levels were associated with increased mortality but not with vascular function or incident CVD [57].

Role of FGF23 in people with chronic kidney disease

Mortality

A prospective study of over 10,000 incident patients with ESKD on HD showed that increased cFGF23 levels were associated with mortality independently of serum phosphate levels and other known risk factors [58]. In a cohort of outpatients with prevalent coronary artery disease in the Heart and Soul study, higher serum cFGF23 levels were independently associated with increased mortality and CV events [59]. In the prospective Chronic Renal Insufficiency Cohort (CRIC) study of patients with CKD stage 2–4, elevated serum cFGF23 was independently associated with mortality [60]. cFGF23 levels were stable in the majority of patients with CKD, but serial measurements identified subpopulations with up to 15 times higher risk of death [61]. In patients with CKD stage 4–5 in the Homocysteine in Kidney and End Stage Renal Disease (HOST) study, serum cFGF23 levels were strongly and independently associated with all-cause mortality, CV events, and initiation of chronic dialysis [62]. This association between elevated cFGF23 and mortality has also been shown in kidney transplant recipients [63].

Cardiovascular disease

Patients with CKD have an increased risk of mortality, and this is driven primarily by increased CV events, both of which increase as eGFR declines [64]. The factors associated with increased CV risk are multifactorial with nontraditional risk factors playing a major role. In the above HOST study, serum cFGF23 levels were strongly associated with myocardial infarction and amputations [62]. In the CRIC study, elevated cFGF23 levels were associated with an increased risk of heart failure but not with atherosclerotic events [65]. Furthermore, in the same cohort, a strong association was found between elevated serum cFGF23 and incident and prevalent atrial fibrillation which was substantially attenuated only by adjustment for LVH, atrial enlargement, and heart failure events [66].

A metaanalysis of FGF23 and risks of CV and non-CV diseases found that a difference in FGF23 levels corresponding to the difference between the top and bottom thirds of baseline FGF23 concentrations was associated with a 30% increased risk of MI and stroke, 40% increased risk of CV mortality, and 50% increased risk of heart failure [67]. The observation that these associations are not observed in disorders with a primary FGF23 excess due to monogenetic diseases suggests that these adverse events are not directly mediated by FGF23 but are due to associated confounding factors.

Left ventricular hypertrophy

LVH is a common complication in patients with CKD and is associated with an increased risk of heart failure, atrial fibrillation, ventricular arrhythmias, and sudden cardiac death. Increased serum cFGF23 levels are associated with LVH in CKD patients [68] and in ESKD patients undergoing MHD [69] and chronic peritoneal dialysis [70]. In CKD patients in the CRIC study, elevated serum cFGF23 levels were shown to be associated with a greater risk of both prevalent LVH and of developing LVH in persons who had normal left ventricular geometry at baseline.

Using animal models, it was shown that FGF23 directly causes cardiac hypertrophy mediated by klotho-independent, FGFR-dependent activation of the calcineurin-NFAT signaling cascade [71]. It was subsequently demonstrated that FGF23 acts on cardiac myocytes via a different receptor, FGFR4, in the absence of its coreceptor in the kidney; that is, klotho. This suggests that selective FGFR4 blockade might be a potential therapeutic strategy to mitigate the cardiac toxicity of FGF23 without interfering with its effect on phosphate homeostasis [17]. FGF23 also induces hemodynamic effects that lead to LVH. These effects may include upregulation of the sodium–chloride cotransporter in the distal convoluted tubule leading to sodium retention and volume overload and increased levels of asymmetric dimethylarginine, a competitive inhibitor of nitric oxide production that impairs vasodilation [15]. In an animal study, circulating klotho deficiency was associated with cardiac hypertrophy and dysfunction; the association of these disorders with FGF23 was only observed when plasma Klotho levels were decreased [72]. A bidirectional effect between cardiac disease and serum FGF23 is suggested by animal models showing that LVH in transgenic mice is associated with an increase in both myocardial and serum intact FGF23 [73].

Vascular calcification and endothelial function

Although increased phosphate levels appear to play a role in the transition of vascular smooth muscle cells (VSMCs) from a vascular to a mineralizing phenotype, the role of FGF23 in this process is not clear. In the CRIC study, baseline cFGF23 levels were not associated with the severity of coronary artery calcium scores. This was in contrast to the association observed between higher serum phosphate and increased coronary artery calcium even after adjustment for cFGF23 levels. In cultured human VSMCs, elevated phosphate concentrations induced calcification in vitro, whereas exogenous FGF23 had no effect on phosphate uptake or phosphate-induced calcification regardless of the phosphate concentration or presence of soluble klotho [74]. CKD is a state of klotho deficiency with a linear decrease in klotho levels as CKD worsens, starting in early CKD [75]. It has been shown in transgenic mice that klotho deficiency causes severe vascular calcification [76]. This process can be ameliorated by klotho, by enhancing phosphaturia, preserving glomerular filtration, and directly inhibiting phosphate uptake by VSMCs.

Progression of chronic kidney disease

Potential mechanisms by which FGF23 excess may enhance the progression of CKD are not completely understood. In the CRIC study, elevated cFGF23 was shown to be an independent risk factor for ESKD in patients with relatively preserved kidney function and for mortality across the spectrum of CKD [60]. Serial cFGF23 measurements showed that increasing FGF23 levels are independently associated with the risk of progression to ESKD [77]. Longitudinal study of this cohort showed that mean serum cFGF23 levels increased markedly in the 5 years before the onset of ESKD, while PTH and phosphate increased modestly, and serum calcium levels declined minimally over time [78]. In a prospective cohort of 984 stable kidney transplant recipients, higher serum cFGF23 levels were independently associated with increased mortality and allograft loss independent of serum phosphate and PTH levels [63]. Despite these epidemiological associations, these studies are limited by residual confounding, and FGF23 may just be a marker of the severity of kidney disease rather than a cause of progressive kidney disease.

Interventions to target lowering of phosphate and FGF23

The aim of lowering serum phosphate is to reduce such long-term adverse outcomes as increased mortality and CV disease in CKD. A decline in serum phosphate levels in MHD patients was associated with improved survival in a multinational prospective cohort [79]. Interventions in nondialyzed CKD patients with normal or slightly increased serum phosphate could be considered preventive rather than therapeutic to ameliorate the onset of the pathological cascade that is associated with CKD-MBD [2]. Since dietary phosphate is the major determinant of FGF23 secretion, interventions to reduce intestinal phosphate absorption should lead to lower FGF23 levels. Direct blockade of FGF23 is an investigational approach to ameliorate the adverse effects of this hormone. The overall approach to management of elevated phosphate is summarized in Fig. 24.4.

Extracorporeal phosphate removal to lower serum phosphate and FGF23

Dialytic removal of phosphate averages ~800 mg per HD treatment session. However, the amount removed varies widely among patients, ranging from 300 to 1200 mg per dialysis even with similar doses of dialysis [81]. The amount of phosphorus removed by HD is not dependent on different serum phosphate concentrations but reflects a marked difference between patients in their rate of phosphorus mobilization, mainly from muscle to blood [82]. In a single-center prospective cohort study, increased frequency of HD with short daily treatments

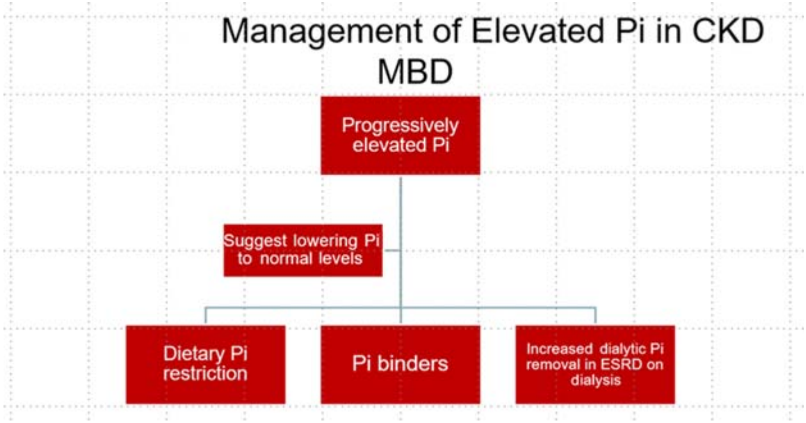
Management of Elevated Pi in CKD MBD
Progressively elevated Pi
Suggest lowering Pi to normal levels
Dietary Pi restriction
Pi binders
Increased dialytic Pi removal in ESRD on dialysis

FIGURE 24.4 Management of elevated Pi in CKD-MBD. *CKD*, Chronic kidney disease; *MBD*, mineral and bone disorder. *Source: Adapted from Kidney Disease: Improving Global Outcomes. KDIGO 2017 clinical practice guideline update for the diagnosis, evaluation, prevention, and treatment of chronic kidney disease-mineral and bone disorder (CKD-MBD). Kidney Int Suppl (2011) 2017;7(1):1–59.*

led to increased phosphate clearance per week and resulted in a decrease in the use of phosphate binders from 77% to 40% at 12 months [83]. Similar improvements in serum phosphate levels with intensive HD were seen in the Frequent Hemodialysis Network (FHN) trial of daily short HD versus conventional HD and in the FHN nocturnal trial [84]. A post hoc analysis of these two trials showed that lower serum phosphate concentrations led to a decrease in serum FGF23 levels, but this has not been examined in large prospective studies [85]. A metaanalysis of randomized controlled trials on convective therapies using hemodiafiltration versus low-flux HD revealed a net increase in phosphate clearance with convective therapies by 20.8 mL/min [86].

Oral phosphate binders

A number of phosphate binders are used clinically to lower intestinal phosphate absorption. This also leads to the upregulation of active sodium phosphate cotransporters (NaPi2b) in the small intestine [87] which, by promoting increased absorption, may limit the effectiveness of the binders in CKD patients. Observational studies have shown a survival benefit in MHD patients who use phosphate binders as compared to those not taking these binders [88–90]. The optimal serum phosphate levels that should be aimed for with binders are not known. This question is the subject of ongoing trials, such as the HiLo pragmatic trial that will compare the effects of different serum phosphate targets in MHD patients (NCT04095039).

The KDIGO CKD-MBD 2017 guidelines update recommends restricting the use of calcium-based binders [91]. This recommendation was based on the reduction in CV mortality and the increased survival observed with the use of noncalcium-based binders [80,92,93]. Although the studies are limited by their small sample size, noncalcium-based phosphate binders given to nondialyzed CKD patients with normal serum phosphate levels appear to lower serum FGF23 more than do calcium-based binders [94–97].

Transcription of FGF23 is reported to be enhanced by iron deficiency [98]. This may provide an opportunity for specific benefits of iron-based phosphate binders. In addition to decreasing intestinal phosphate absorption and providing iron to the body, these binders, by increasing body iron, may reduce FGF23 transcription and thereby decrease FGF23 levels. In a rat model of CKD, sucroferric oxyhydroxide decreased iFGF23 to a significantly greater degree than lanthanum carbonate or sevelamer hydrochloride [99]. A pilot study of MHD patients with hyperphosphatemia showed that treatment with sucroferric oxyhydroxide rapidly reduced serum phosphate with a concomitant decrease in serum FGF23 levels and led to the improvement in anemia with a decreased need for intravenous iron and erythropoiesis-stimulating agents [100].

In a mouse model of CKD, initiation of ferric citrate treatment early in the course of murine CKD lowered iFGF23, slowed CKD progression, improved cardiac function, and significantly improved survival [101]. In nondialyzed CKD patients, ferric citrate can also be used to treat iron deficiency. Short-term use of ferric citrate in CKD 3–5 patients with iron deficiency anemia and serum phosphate >4 mg/dL can replete iron stores, decrease serum phosphate, and reduce serum iFGF23 and cFGF23 [102]. A pilot study showed that the prescription of fixed-dose ferric citrate coordination complex to patients with eGFR ≤20 mL/min per 1.73 m^2 resulted in significant improvements in anemia-related end points and significant reductions in serum phosphate and iFGF23 [103].

Novel interventions to reduce intestinal phosphate absorption

Nicotinamide, a derivative of niacin, has been shown in high doses to inhibit NaPi2b expression in animal models [104,105]. In MHD patients the use of nicotinamide has been shown to reduce serum phosphate levels comparably to phosphate binders [106] and has an additive effect when given in combination with phosphate binders [107]. In the AIM-HIGH trial the use of extended release niacin in the subset of patients with CKD lowered serum phosphate but did not lower iFGF23 at 3 years [108]. The CKD optimal management with binders and nicotinamide (COMBINE trial) was a randomized trial to test the efficacy and safety of nicotinamide and lanthanum carbonate in isolation or in combination in persons with CKD stage 3b−4. It failed to significantly lower serum phosphate or iFGF23 levels in any intervention group at 12 months [109].

Tenapanor is a nonabsorbable inhibitor of the sodium-hydrogen exchanger 3 (NHE3) in the intestine which has been used to target the predominant mechanism of enteral phosphate absorption via paracellular transport. It blocks NHE3-dependent sodium absorption leading to decreased proton secretion by enterocytes. The reduced intracellular pH leads to a decrease in the permeability of the tight junctions, which, in turn, reduces paracellular phosphate absorption. Short-term use of tenapanor led to dose-dependent reductions in serum phosphate in MHD patients with hyperphosphatemia [110,111]. In one of these studies, following a marked increase in serum iFGF23 in response to withdrawal of phosphate binders, tenapanor significantly decreased serum iFGF23 [112].

Calcimimetics

Calcimimetics are allosteric activators of the calcium-sensing receptor and reduce iPTH by increasing the sensitivity of the parathyroid gland to serum calcium. In animal models the calcimimetic cinacalcet decreases serum PTH, 1,25-VitD, and iFGF23 leading to hypocalcemia and hyperphosphatemia [113]. In ESKD patients, hyperphosphatemia does not occur in response to cinacalcet treatment, because urinary phosphorous cannot increase substantially in response to the reduction in serum FGF23 and PTH. The use of cinacalcet to treat SHPT in MHD patients has been shown to decrease iFGF23, whereas vitamin D analogs (another treatment for SHPT) increase FGF23; this effect was independent of the modification of PTH [114]. Etelcalcetide is an intravenous calcimimetic recently approved for the treatment of SHPT in MHD patients. It has been shown to reduce serum PTH and iFGF23 more than placebo or cinacalcet in combination with standard-of-care treatment [115]. In a secondary analysis of these trials, etelcalcetide-mediated reductions in iFGF23 were associated with a decrease in serum calcium, phosphate, and the calcium-phosphate product, but not in PTH. However, the association between the decrease in serum iFGF23 and markers of bone turnover was of borderline and inconsistent significance [116].

Nutritional management of phosphate and FGF23 excess in chronic kidney disease

There have been no large randomized controlled interventional trials that have tested the effects of modifying dietary phosphate intake or treating to obtain normal serum phosphorus levels on outcomes in any population [82]. However, the prevention and treatment of elevated serum phosphate remain a cornerstone of the management of CKD-MBD.

Sources of dietary phosphate

Phosphate is ubiquitous in nearly all animal- and plant-derived foods. The content and bioavailability of phosphate in foods and in other sources of ingested phosphate are highly variable. The three major sources of dietary phosphate are the phosphate present naturally in food, phosphate added to food during processing, and phosphate contained in medications and supplements.

Organic phosphate

For most adults, approximately 20%−30% of dietary phosphorus is obtained from milk and milk products and 20%−30% from meat, poultry, fish, and grains. Naturally occurring phosphates are present mostly as phosphoproteins, phosphate esters, phytates, or phospholipids. These natural sources of phosphate are related to the protein content of these foods and are often referred to as organic sources of phosphate. Vegetables and grains contain a lower amount of phosphate as compared to most meats and milk products [117]. In MHD patients a high protein intake that may be prescribed to prevent or treat protein malnutrition with a concurrent low phosphate intake is associated with the lowest mortality [118]. Thus it is useful to use the ratio of phosphate-to-protein content (mg/g) in protein sources for dietary education, since a lower ratio will lead to lower phosphate intake with adequate protein intake. The lowest ratio is seen with certain animal-derived foods (average, 11 mg phosphate per g protein), including egg whites and pork rinds, whereas whole eggs, dairy products, legumes, and lentils have higher ratios (average 20 mg/g) [119].

Plant-based phosphate in vegetables, grains, and legumes is largely bound to phytates. This phosphate is not as well absorbed as animal-based phosphates because the human intestine does not secrete phytase, the enzyme that hydrolyzes phytate, thereby freeing phosphate for absorption [117]. Thus, while on average about 60% of dietary phosphate is absorbed by the intestinal tract, this may be lower in people who are vegetarian or ingesting mostly plant-based diets.

Phosphate additives and inorganic phosphates

The use of processed foods in the modern world has allowed for increased accessibility, increased shelf life, palatability, and convenience. Processed foods commonly have a high phosphate content because of the use of phosphates as a food additive. The most common additives are sodium phosphate, potassium phosphate, calcium phosphate, and salts of orthophosphoric acid diphosphate, triphosphate, and polyphosphate. These are added to food as preservatives, acidifying agents, emulsifying agents, stabilizers, and taste intensifiers [10]. The absorption of phosphate from additives can be as high as 80%−100% compared to 40%−60% from natural foods. The addition of yeast, a leavening agent that contains phytase, leads to further release of phosphate from plant-based foods. This can result in increased phosphate absorption from plant-based foods that normally have low phosphate bioavailability [119]. The phosphorus content in processes foods includes phosphorus naturally found in these food products plus the phosphorus content in the additives, which may increase the total phosphorus intake to 1000 mg/day [117,120]. In Western diets, phosphate additives have been shown to contribute 10%−50% of total phosphate intake [121]. This may be intensified in people from lower socioeconomic groups because they often have an increased proportion of processed foods in their diets [122]. However, a cross-sectional analysis from the MESA cohort did not show that greater intake of foods commonly enriched with phosphate additives was associated with higher serum phosphate levels in people with largely preserved kidney function [123].

Phosphate-containing excipients, used in the formulation of drugs, are found in approximately 11% of frequently used medications. These pose an additional source of phosphate intake that becomes even more significant in patients with kidney disease who have multiple comorbidities and may take many medicines [124].

Inadequacy of food labels and regulatory policy

A major public health challenge with regard to avoiding excessive dietary phosphate intakes is that phosphate content is not mandated on food labels. Phosphate additives fall under the category of food items that are generally regarded as safe and hence are not required under the mandatory labeling according to the Food, Drug and Cosmetic Act. Furthermore, currently available food composition tables in books and software programs do not accurately reflect the additional phosphate contained in phosphate additives. The FDA published the updated version of the Nutrition Facts Panel (NFP) in May 2016 [125]. Despite multiple requests, the FDA declined to require phosphate content on the label, because the label is not intended for clinical management of chronic diseases. Implementation of mandatory labeling of phosphate content on packaged foods, drugs, and dietary supplements would help develop reliable dietary assessment tools and guide appropriate diet choices for patients with kidney disease [82]. As indicated earlier, the excessive phosphate intake of many normal people might also adversely affect their health.

Dietary therapy for CKD-associated hyperphosphatemia and FGF23 excess

Traditionally, the indication for control of serum phosphate in CKD patients has been to prevent SHPT and associated bone disease. The emerging evidence for other adverse effects of phosphate in CKD suggests that dietary phosphate restriction could help preserve kidney function, reduce progression of vascular calcification, reduce LVH, decrease serum FGF23, and prevent worsening SHPT. Observational studies of the relationship between dietary phosphate intake and death have shown an elevated risk of mortality with both extremes of dietary phosphate intake [118,126].

Intervention trials of changing intake of phosphate additives have shown mixed results. In a crossover trial in adults with early CKD, increasing phosphate intake by raising consumption of phosphate additives did not increase albuminuria or serum FGF23 levels [127]. A randomized control trial of limiting intake of phosphorus-containing food additives on serum phosphate in ESKD patients led to a decline of 0.6 mg/dL in the intervention group [128]. In patients receiving MHD for >6 months, replacing phosphorus-containing food additives with foods without phosphate additives reduced serum phosphate by an average of 2.2 mg/dL without interfering in the nutritional status [129]. Thus patients with ESKD may benefit more from this intervention.

Due to the potential for lower phosphate absorption with plant-based diets, these diets have been recommended for prevention and treatment of hyperphosphatemia. Although plant-based protein has been shown to help preserve kidney function, this effect could be due to differences in amino acid intake, dietary acid load, or phosphate bioavailability [6]. A crossover pilot trial was conducted to directly compare vegetarian and meat diets with equivalent nutrient composition. This study, conducted in nine patients with a mean estimated GFR of 32 mL/min, led to lower serum phosphorus and FGF23 levels with the vegetarian diet [130].

Prior guidelines have recommended that patients with CKD stage 3−5 should limit phosphate intake to 800−1000 mg/day as part of the strategy to manage hyperphosphatemia. This intervention has given inconsistent results, and its effectiveness, therefore, has not been proven. This amount of dietary phosphate is higher than the current recommended dietary allowance for the adult general population, that is, 700 mg/day. According to the KDOQI and Academy of Nutrition and Dietetics (AND) Clinical Practice Guidelines for Nutrition in CKD: 2020 Update, in adults CKD stage 3−5 and MHD patients, it is recommended to adjust dietary phosphate intake to maintain serum phosphate levels in the normal range without specifying a target amount [131]. This is similar to the recommendations in the most recent KDIGO guidelines on CKD-associated MBD [80]. It is also suggested that the bioavailability of dietary phosphate sources be considered although this is not supported by clinical evidence [131]. The guidelines advises selecting commercial foods prepared without phosphate-containing additives, choosing natural foods that have low phosphate-to-protein ratios and preparing foods at home using wet cooking methods which can remove up to 50% of the phosphate content of foods [132−134].

Although dietary phosphate restriction may be used by itself in patients with CKD stage 3−4, the reduction serum phosphate achieved is modest. In most if not all CKD stage 5 patients and in chronic dialysis patients, other interventions must be used in conjunction with dietary phosphate restriction. Short-term dietary phosphate restriction tends to reduce serum FGF23 levels in patients with moderately decreased kidney function [135]. This is observed only with very low phosphate diets (<750 mg/day); lowering of serum FGF23 usually requires concomitant use of phosphate binders and very low phosphate diets for a prolonged duration of time [90,136].

Direct blockade of FGF23 activity

Burosumab, a fully human monoclonal IgG1 antibody against FGF23, was recently approved for the treatment of X-linked hypophosphatemia. It binds circulating intact FGF23 and thereby blocks its biologic effects in target tissues. In an open-label phase II trial in children with X-linked hypophosphatemia, treatment with burosumab improved kidney tubular phosphate reabsorption, serum phosphate levels, linear growth, and physical function and reduced pain and the severity of rickets [137]. Subsequently, in a randomized phase III trial enrolling children aged 1−12 years with X-linked hypophosphatemia, significantly greater clinical improvement was shown in the severity of rickets and in growth, and biochemistries in the patients treated with burosumab as compared with those continuing on conventional therapy [138].

Two studies have explored the utility of anti-FGF23 antibodies in experimental CKD. In rats with antiglomerular basement membrane nephritis and CKD stage 2−4, a single injection of monoclonal mouse antihuman FGF23 antibody was associated with a decrease in serum PTH and an increase in serum phosphorus and 1,25-VitD levels [27]. In 5/6 nephrectomized rats with CKD stage 3−4 given a high-phosphorus diet the use of an antirat FGF23 antibody three times per week for 6 weeks led to sustained decreases in serum PTH, increases in 1,25-VitD levels, and normalization of bone markers. This response was associated with dose-dependent hypercalcemia, marked hyperphosphatemia, aortic calcification, and increased mortality without an effect on ventricular hypertrophy [139]. This paradoxical effect, despite the FGF23 blockade, was attributed to the deleterious effects of hyperphosphatemia, possibly enhanced by the high phosphate diet fed to the rats and progression of kidney failure. It has been speculated that in humans with ESKD, FGF23 blockade in combination with other measures to treat hyperphosphatemia (i.e., dietary and pharmacologic restriction of phosphorus intake and extracorporeal removal of phosphorus) may mitigate or prevent LVH and decrease mortality [140]. However, increased 1,25-VitD with FGF23 blockade might lead to enhanced intestinal absorption of calcium and phosphate and prevent this hypothetical benefit.

Future development of selective FGFR4 antibodies could theoretically abrogate the off-target effects on cardiac myocytes and hepatocytes without affecting phosphate balance. Another theoretical approach would be to use exogenous soluble klotho to bind FGF23 in circulation and minimize activation of klotho-independent pathways.

Summary

The discovery of FGF23 and its role in rare disorders of hypophosphatemic rickets has led to a rapid expansion in our understanding of its effects on the kidney and the pathways that lead to normal mineral metabolism and its dysregulation in CKD. A wide array of epidemiological data supports the association of elevated serum FGF23 with adverse clinical outcomes. Further research into potential targeted interventions is needed to improve outcomes. Nutritional management of phosphate remains the cornerstone of management of CKD-associated MBDs.

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CHAPTER

25

Vitamin D in kidney disease

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Introduction

Vitamin D is a steroid hormone that interacts with the vitamin D receptor (VDR) complexes to affect a broad range of cellular functions [1]. Its most classic functions are in the gastrointestinal tract to promote calcium and phosphorus absorption, in the kidney to promote calcium reabsorption, and in bone to promote the development of osteoclasts that resorb bone. The role of vitamin D in kidney disease has been well recognized since the early 1970s [2,3], but our understanding continues to evolve [4]. Vitamin D is metabolized to both active and inactive compounds in the proximal tubule of the kidney, setting off a cascade of physiologic pathways influencing calcium homeostasis and bone disease. With growing recognition of nonclassical targets of vitamin D and its metabolites, the role of vitamin D in many additional pathways relevant to kidney disease has been postulated. Potential pathways include contributions to hypertension, insulin resistance, cardiovascular complications, and kidney disease progression [5–7]. This chapter will discuss normal vitamin D physiology, including the prominent role of the kidneys in vitamin D metabolism, and our current understanding of the role of dietary and supplemental vitamin D for patients with kidney disease.

Normal vitamin D metabolism and functions

Intake and metabolism of vitamin D

Vitamin D is obtained through diet and supplements or produced endogenously after contact with ultraviolet B radiation in sunlight. Vitamin D comes in two major forms, vitamin D_2, or ergocalciferol, and vitamin D_3, or cholecalciferol (Table 25.1) [8]. After ingestion and absorption, vitamin D of either form is converted by cytochrome P-450 enzymes in the liver, such as CYP2R1, to 25-hydroxyvitamin D (25-D) [9]. Conversion in the liver is rapid and unregulated; thus 25-D is the major storage form of vitamin D and currently the most appropriate indicator of vitamin D status in the general population. The vast majority of 25-D circulates in the bloodstream bound to vitamin D–binding protein (VDBP) or albumin [9,10].

Although 25-D is the primary storage form and the target of supplementation, the most potent and active form of vitamin D is 1,25-dihydroxyvitamin D (1,25-D). Like 25-D, 1,25-D can be formed from either D_2 or D_3 and will be referred to collectively throughout this chapter. 1,25-D is formed from 25-D as the result of hydroxylation at the lead (1α) carbon. 1α-Hydroxylation is primarily performed by the cytochrome P-450 enzyme in the mitochondria of the proximal tubule of the kidney, encoded by CYP27B1 [3,11]. First, VDBP or albumin-bound 25-D is reabsorbed in the kidney proximal tubule through specific receptors, megalin and cubilin [12–14]. After absorption, 25-D is converted locally to 1,25-D and reabsorbed into the circulation to exert its hormonal functions. Unlike 25-hydroxylation, conversion to 1,25-D is a highly regulated process. Control is exerted on two major steps: (1) 1α-hydroxylation by CYP27B1, which produces active 1,25-D, and (2) 24-hydroxylation by CYP24A1, which metabolizes 25-D and 1,25-D to the inactive metabolites 24,25-D or 1,24,25-D (Fig. 25.1) [9,15,16].

Regulation of 1,25-D production and catabolism is under hormonal control by parathyroid hormone, fibroblast growth factor-23, and 1,25-D itself. Parathyroid hormone is a hormone released by the parathyroid gland in response to falling blood calcium levels. Parathyroid hormone restores calcium levels by

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TABLE 25.1 Forms and major sources of vitamin D.

Vitamin D form	Common name	Common sources	Comments
Vitamin D_2	Ergocalciferol	Fungal foods: mushrooms, yeast	Intake form
Vitamin D_3	Cholecalciferol	Sunlight, fatty fish, cod liver oil, egg yolk, supplemented foods	Intake form
25-Hydroxyvitamin D (25-D)	Calcidiol	Liver hydroxylation of D_2 or D_3	Major circulating form
1,25-dihydroxyvitamin D (1,25-D)	Calcitriol	Kidney hydroxylation of 25-D	Highly potent active form
24,25-Dihydroxyvitamin D (24,25-D)	–	Catabolic hydroxylation of 25-D	Inactive form
1,24,25-Trihydroxyvitamin D (1,24,25-D)	Calcitroic acid	Catabolic hydroxylation of 1,25-D	Inactive form

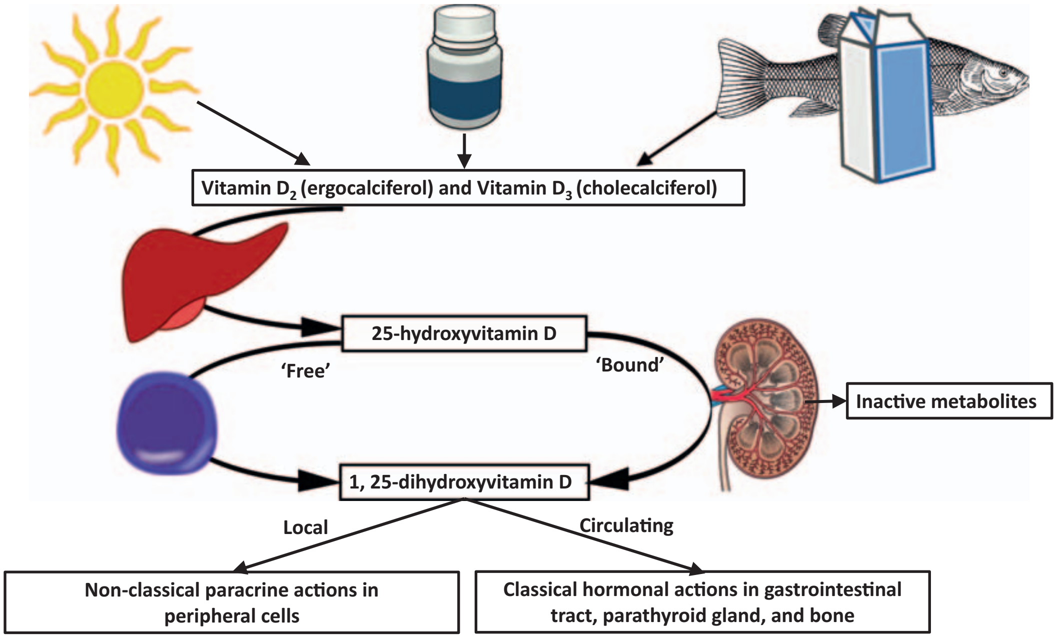
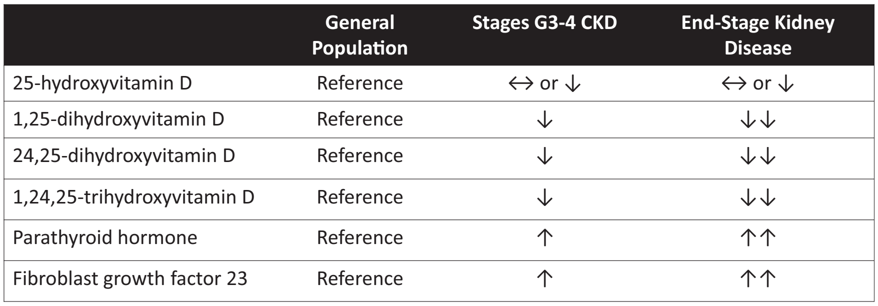

Vitamin D₂ (ergocalciferol) and Vitamin D₃ (cholecalciferol)
25-hydroxyvitamin D
'Free'
'Bound'
Inactive metabolites
1, 25-dihydroxyvitamin D
Local
Circulating
Non-classical paracrine actions in peripheral cells
Classical hormonal actions in gastrointestinal tract, parathyroid gland, and bone

FIGURE 25.1 **Simplified overview of normal vitamin D metabolism.** Vitamin D is produced in the skin by conversion of 7-dehyroxycholesterol to cholecalciferol in response to ultraviolet B radiation or from the consumption of vitamin D–containing foods and supplements. Cytochrome P-450 enzymes in the liver rapidly convert vitamin D to 25-hydroxyvitamin D, the major circulating form. Most 25-hydroxyvitamin D circulates complexed to VDBP or albumin, which improves its stability and promotes uptake in the kidney via megalin and cubilin proteins. The 1α-hydroxylase enzyme, primarily expressed in the kidney, then converts 25-hydroxyvitamin D to its most active form 1,25-dihydroxyvitamin D and releases it into the circulation for hormonal functions in target tissues. The kidney also expresses 24-hydroxylase that catabolizes both 25-hydroxyvitamin D and 1,25-dihydroxyvitamin D to inactive forms. Peripheral cells, including white blood cells, can also locally convert 25-hydroxyvitamin D to 1,25-dihydroxyvitamin D allowing it to bind the vitamin D receptor complex and function as a transcription factor locally. "Free" or unbound 25-hydroxyvitamin D may be more effectively taken up by peripheral cells because it can freely cross cell membranes, although controversy on this point remains. Hundreds of genes have been shown to have a vitamin D–responsive element in their promoter. Not all of these functions are well understood. For kidney image: Artwork by Holly Fischer/CC BY (https://creativecommons.org/licenses/by/3.0). *VDBP*, Vitamin D–binding protein.

increasing calcium absorption in the gastrointestinal tract, reabsorbing calcium in the kidney, and mobilizing calcium from bone stores. One mechanism through which parathyroid hormone promotes these actions is by stimulating 1α-hydroxylation and inhibiting 24-hydroxylation to raise biologically active 1,25-D levels [17]. In contrast, the bone-derived hormone fibroblast growth factor-23 rises in response to increased levels of 1,25-D and helps lower or stabilize levels by limiting transcription of 1α-hydroxylase and increasing transcription of 24-hydroxylase [9,16,17]. 1,25-D and 25-D may also induce expression of 24-hydroxylase to



	General Population	Stages G3-4 CKD	End-Stage Kidney Disease
25-hydroxyvitamin D	Reference	↔ or ↓	↔ or ↓
1,25-dihydroxyvitamin D	Reference	↓	↓↓
24,25-dihydroxyvitamin D	Reference	↓	↓↓
1,24,25-trihydroxyvitamin D	Reference	↓	↓↓
Parathyroid hormone	Reference	↑	↑↑
Fibroblast growth factor 23	Reference	↑	↑↑

FIGURE 25.2 **Levels of vitamin D, its metabolites, and major regulatory hormones in patients with chronic kidney disease.** Depicted are major active and inactive metabolites of vitamin D_2 (ergocalciferol) and vitamin D_3 (cholecalciferol). Description of major changes in metabolites and regulatory hormones in kidney disease are provided.

control their production [18]. Together these important regulatory steps prevent vitamin D toxicity and maintain vitamin D sufficiency under conditions of varying intake and sun exposure.

Both 1α-hydroxylase and 24-hydroxylase activity may be reduced in patient with chronic kidney disease (CKD) because the kidney is the primary site of these enzymatic activities. Thus even with normal stores of 25-D, patients with moderate-to-advanced CKD tend to have lower levels of biologically active 1,25-D and the inactive vitamin D metabolites, 24,25-D and 1,24,25-D (Fig. 25.2) [19]. What exactly these metabolites might mean clinically is an area of ongoing investigation. Lower ratios of 24,25-D to 25-D are associated with increased mortality in patients with kidney disease, potentially because these relatively low 24,25-D levels reflect low 1,25-D, low 25-D or because of residual correlation with kidney function leading to confounding [20,21].

Normal functions of vitamin D in bone mineralization

Vitamin D is a critical hormone-regulating bone mineralization by calcium and phosphorus. Vitamin D contributes to this process by ensuring adequate absorption of these mineral ions from the gastrointestinal tract [22,23]. Underscoring this key role, deficiency of vitamin D due to insufficient diet, inadequate sun exposure, or genetic defects in vitamin D function results in rickets and osteomalacia, bone diseases characterized by impairment of growth in children, and inadequate mineralization of the skeleton at all ages [24–26]. These conditions can generally be reversed or prevented by restoration of vitamin D stores and adequate daily intake of vitamin D. Additionally, genetic conditions in which vitamin D metabolism is impaired can typically be overcome by high dose supplementation with calcium and phosphorus, implying that ensuring absorption of these minerals at typical intake levels is a central role of vitamin D [11,15].

In the gastrointestinal tract, 1,25-D promotes active mineral absorption through enterocytes [22,23]. Throughout the small and large intestines, 1,25-D binds to the VDR forming a transcriptionally active complex [1]. This complex interacts with vitamin D–responsive elements in nuclear DNA to increase the transcription of critical transporters that support absorption of calcium and phosphorus. Increased transcription of the protein calbindin helps sequester calcium inside cells and, by increasing its concentration gradient, promotes further intestinal calcium absorption. Relevant transporters and proteins involved in calcium and phosphorus absorption that have been shown to be responsive to 1,25-D include transient receptor potential vanilloid 6 (TRPV6) and the Ca^{2+}-ATPase PMAC1 for calcium and sodium-dependent phosphate cotransporter 2b (NPT2b; Table 25.2) [27,28].

TABLE 25.2 Selected proteins induced by 1,25-dihydroxyvitamin D yielding classical effects of vitamin D.

Target tissue	Protein	Effect
Gastrointestinal	TRPV6, calbindin, PMCA1	Increased active luminal calcium absorption
Gastrointestinal	NPT2b	Increased active luminal phosphorus absorption
Kidney	TRPV5, TRPV6, calbindin	Increased active calcium reabsorption from the glomerular filtrate
Bone	RANKL	Mobilize bone mineral by stimulating osteoclasts

RANKL, Receptor activator of nuclear factor kappa beta ligand; TRPV5, transient receptor potential vanilloid 5; TRPV6, transient receptor potential vanilloid 6.

In the kidney, 1,25-D promotes reabsorption of calcium and, hence, prevents excess losses in the urine. After being filtered at the glomerulus, calcium is reabsorbed heavily in the proximal tubule of the kidney along with bulk transport of salt and water. Finer regulation of calcium excretion occurs in the thick ascending limb and distal tubule through calcium transporters, such as transient receptor potential vanilloid 5 (TRPV5), calcium ATPases, and Na/Ca exchangers [15]. At these sites, complexes of 1,25-D and its receptor stimulate transcription of proteins involved in reclamation of calcium from the tubular filtrate. Vitamin D–responsive proteins involved in calcium transport in the kidney include calbindins, TRPV5, and TRPV6 (Table 25.2).

1,25-D has additional effects in bone, which primarily promote bone resorption and mineral release. Specifically, 1,25-D and VDR complexes stimulate transcription of the receptor activator of nuclear factor kappa beta ligand (RANKL) among other bone regulatory proteins (Table 25.2) [28]. RANKL is a factor that stimulates maturation of undifferentiated osteocytes into mature osteoclasts that resorb bone. Through this pathway the direct effect of 1,25-D on bone may be to promote resorption, a process that liberates calcium and promotes remodeling. Bone remodeling can help ensure healthy bone structure through new bone synthesis but can also lead to bone loss if excessive.

Nonskeletal actions of vitamin D

In addition to its classical hormonal functions on the skeleton, there is an increasing recognition of autocrine and paracrine functions of vitamin D in a variety of cell types. Hundreds of genes are influenced by a vitamin D–responsive element [29]. These genes include those involved in immunity, cell survival, blood pressure regulation, and insulin sensitivity, suggesting potentially broad impacts of vitamin D status on physiological processes that go beyond mineral and bone [29,30]. Some of the most well-established effects of vitamin D are on the innate and adaptive immune systems and the renin–angiotensin system that regulates blood pressure and the glomerular filtration rate in the kidney [31–33]. As a result of these pleiotropic actions, vitamin D deficiency has been implicated in the pathogenesis of numerous autoimmune and infectious conditions, metabolic disease, and cancer [5,34,35]. Some studies investigating genetic polymorphisms in vitamin D pathways also implicate these pathways in the risk of cancer, cardiovascular disease, multiple sclerosis, type 1 diabetes, and skin diseases such as psoriasis, among others [36–40]. To date, rigorous interventional studies do not strongly support treatment with vitamin D for these indications [34,41].

Vitamin D binding protein and the free hormone hypothesis

Although 25-D bound to VDBP or albumin is most efficiently absorbed and hydroxylated to 1,25-D in the kidney, in other tissues “free” 25-D that is not bound to VDBP or albumin may more effectively enter the cell [21]. Because of its hydrophobicity, “free” 25-D can cross cell and nuclear membranes to interact directly with the VDR and influence cellular functions in a wide variety of cell types. It is hypothesized, but not proven, that “free” 25-D may be the most relevant form for vitamin D’s autocrine and paracrine effects (Fig. 25.1) [42]. In some studies, “free” 25-D levels correlate more strongly with parathyroid hormone as well, suggesting that “free” 25-D may also be the more active form controlling parathyroid responses [43]. Not all studies support this concept, and more research is needed to fully test this hypothesis and elucidate the potentially distinct effects of bound and “free” 25-D [44]. If true, VDBP may then play an important role in sequestering vitamin D and helping to regulate its activity. Interventional studies have shown that supplementation with high-dose vitamin D raises VDBP levels, which presumably may help to control activity in the vitamin D axis [18]. Another important role of VDBP may be to maintain a stable reservoir of vitamin D.

Genetics and heterogeneity of vitamin D metabolism

Some support for the free hormone hypothesis comes from genetic studies related to polymorphisms in VDBP. VDBP has been known for decades to have different genetically determined isoforms, each of which has a different binding affinity for vitamin D that results in different circulating total 25-D levels [36,45–47]. Some genetic mutations in the GC gene that encodes VDBP are differentially distributed across different ancestral groups. For instance, the more common single-nucleotide variant (SNP) at rs7041 in individuals of African ancestry results in a VDBP with lower affinity for vitamin D and may result in higher “free” 25-D levels at the same level of total 25-D. An SNP at rs4855 is another commonly described variant that can affect VDBP affinity for 25-D.

Several studies have shown that 25-D levels associate more strongly with outcomes such as mortality and cardiovascular disease in patients of European compared with African descent [48–50]. In addition, African-Americans tend to have higher levels of parathyroid hormone, higher bone density, and different relationships between vitamin D, parathyroid hormone levels, and bone anatomy or metabolism [46,51–55]. It has been postulated that these phenotypic differences may be related to different frequencies of GC gene polymorphisms that modify the proportion of total 25-D that is “free” in different ancestral groups [56,57]. To date, this hypothesis has not been strongly confirmed, and several studies do not support differences in the relationships between total and “free” 25-D by race [58].

Other polymorphisms in vitamin D pathway genes, such as the VDR, have also been shown to modify associations between 25-D levels and clinical outcomes in a Caucasian population [52]. More work is needed to fully understand differences in 25-D biology according to genotype and to determine if genetically personalized targets or supplementation strategies are needed.

Vitamin D physiology in CKD

Vitamin D metabolism and action is significantly altered by the presence and severity of CKD. As kidney function worsens, circulating levels of both parathyroid hormone and fibroblast growth factor-23 rise [59]. Both of these hormones play an important role in controlling phosphorus homeostasis in CKD by reducing reabsorption of phosphorus in the proximal tubule of the kidney. Increasing levels of these hormones ensure that the kidney is better able to excrete the daily phosphorus load from the diet despite a lower glomerular filtration rate [17]. The prevailing scientific theory postulates that these hormones initially rise to enable phosphorus clearance but have other effects that impair vitamin D metabolism [60,61]. Fibroblast growth factor-23 inhibits the 1α-hydroxylase enzyme and induces 24-hydroxylase resulting in more catabolized 25-D and lower 1,25-D levels in kidney disease [19,62]. As 1,25-D levels fall, the further rise in secreted parathyroid hormone maintains circulating calcium concentrations, but with the consequence of secondary hyperparathyroidism.

Secondary hyperparathyroidism is present in the majority of patients with advanced CKD and end-stage kidney disease. When left untreated, severe secondary hyperparathyroidism results in severe skeletal and growth abnormalities, including bone fragility and fracture, bone tumors, and vascular calcification [63–65]. Interrupting this cascade with supplementation of 1,25-D is one of the most effective methods to prevent and treat severe secondary hyperparathyroidism [66].

Detailed sources of vitamin D and burden of vitamin D deficiency

Vitamin D is an essential nutrient obtained through both dietary and nondietary means. Dietary forms of vitamin D are primarily in the form of vitamin D_2, or ergocalciferol, and vitamin D_3, also known as cholecalciferol. Ergocalciferol is a natural plant-based sterol found commonly in mushrooms and many fortified foods in the United States, such as milk, yogurt, and orange juice. Cholecalciferol is a natural animal-based sterol. High levels of cholecalciferol can be found in oily fish, such as salmon, mackerel or cod liver oil, egg yolks, or is generated endogenously in the skin by the action of ultraviolet B radiation on 7-dehydrocholestrol in the dermis [8].

In adults the recommended dietary allowance of vitamin D ranges from 600 to 800 IUs daily, an intake that is anticipated to yield a circulating 25-D level of at least 20 ng/mL if sun exposure is minimal [67]. These ranges were most recently evaluated and set by the Institute of Medicine (IOM) in 2011 based on optimal levels to maintain bone health for the majority of the population [68,69]. The IOM established the upper tolerable limit at 4000 IUs daily based on such anticipated toxicity as elevated blood and urine calcium, kidney stones, and other extraskeletal calcification [70–73]. However, the IOM targets are not without controversy, and many experts consider these intakes and targets too low [74]. Expert review by the Endocrine Society recommends a level of at least 30 ng/mL for maintenance of bone mineral density and prevention of osteomalacia. This target corresponds to a recommended intake of 1500–2000 IUs daily for adults, with higher intakes for obese adults who sequester 25-D in adipose tissue and have lower levels [75]. A variety of studies evaluating associations between 25-D levels and markers of bone health, including bone mineral density, osteomalacia, and biochemical responses such as rising serum parathyroid hormone, generally support these targets [59,76–78].

In CKD patients, studies estimate that vitamin D insufficiency or deficiency is common, present in about 40%–50% or more of patients [59,79,80]. Prevalence of vitamin D deficiency is modestly higher among those with more advanced disease [79–82]. These estimates depend on the serum cut points used for deficiency, and experts do not unanimously agree [83]. Most of the aforementioned estimates utilize the cut points for insufficiency of <30 ng/mL and deficiency of <15–20 ng/mL as recommended by the Endocrine Society guidelines [75]. Using the IOM-derived serum cut point of 20 ng/mL for sufficiency, the rates of insufficient 25-D at the population level are significantly lower and decreasing over time [70,72,84]. Additionally, many of these studies are conducted in convenience samples and not necessarily nationally representative groups. Nonetheless, CKD patients may be more likely to have vitamin D deficiency as compared to the general population.

Reasons for high rates of 25-D deficiency are multifactorial but may include effects of proteinuria causing loss of vitamin D bound to VDBP in the urine, poor health status with reduced exposure to sunlight, and limited dietary intake. Other risk factors for deficiency in the general population include obesity with sequestration of 25-D in adipose tissue, dark skin pigmentation resulting in less production in the skin, less sun exposure due to geographic locations or institutionalization, and medications that induce cytochrome P-450 enzymes resulting in increased vitamin D catabolism [8,56,85–88]. Due to the defect in 1α-hydroxylation in the diseased kidney, deficiency of the active 1,25-D form is pronounced and strongly linked to kidney function in patients with CKD [81].

Outcomes associated with vitamin D deficiency

Observational studies support associations of low 25-D with a wide variety of adverse outcomes, including cardiovascular disease, insulin resistance, cancer, and mortality [5,89]. Several of these studies were conducted in the CKD population [89]. Limitations of most of these latter studies include confounding by dietary intake, physical activity, and health status; hence, making clear conclusions about the cause-and-effect nature of these relationships is problematic. Mendelian randomization is a method that leverages genetically determined differences in vitamin D levels to examine the associations between vitamin D levels and clinical outcomes. These methodological designs can be effective, because the differences in vitamin D levels are due to variations in genes and not to other factors, like lifestyle, that may be difficult to identify or measure. Several Mendelian randomization studies support potentially cause-and-effect relationships between low 25-D and mortality [90]. Although Mendelian randomization is a strong study design, it still may have bias if ancestral background is not well accounted for in the analysis or if there are pleiotropic effects of the genes that could impact outcomes by other pathways.

Clinical trials remain the strongest design to definitively support cause-and-effect relationships. These trials are not always possible to conduct due to cost, the challenges of treating individuals for long periods of time, or the ethical dilemma of withholding treatment when it may be clinically indicated for other reasons such as bone health. With these caveats in mind, clinical trials of vitamin D supplementation have not confirmed these foregoing associations as clearly causal [5]. A recent trial of supplementation with 4000 IU daily of cholecalciferol versus placebo, the D2D trial, did not indicate a benefit to vitamin D supplementation. Patients in this trial were at risk for diabetes based on glucose intolerance but did not necessarily have vitamin D deficiency at baseline. However, in post hoc analyses, patients with severe vitamin D deficiency (25-D $<$ 12 ng/mL) who received supplementation did have a lower risk of incident diabetes mellitus [91]. In the DDM2 trial, supplementation with 4000 IU daily of cholecalciferol did not improve insulin secretion or glycemic control in patients with type 2 diabetes [92]. In the large VITAL trial, supplementation of adults with 400 IU daily of cholecalciferol did not reduce the overall risk of cardiovascular events or new diagnoses of cancer. Prior observational studies more strongly implicated vitamin D deficiency as being associated with poor cancer outcomes as opposed to being associated with new diagnoses of cancer [90]. With this in mind, secondary analyses of VITAL suggested a possible benefit of supplementation on death from cancer, but this result was not prespecified and should be viewed as exploratory [93]. Similar null results were observed for cancer and cardiovascular outcomes in the Vitamin D Assessment Study; but in this study, high doses of vitamin D supplementation were used [93–95]. For bone outcomes, such as bone mineral density and fracture, benefits have also not been clearly demonstrated at all sites [96–101]. Some studies even show evidence for harm with high-dose vitamin D supplementation, with reduction in bone density and increase in fracture and falls [102,103]. The authors hypothesize that this paradoxical effect is due to excessive stimulation of osteoclastic bone resorption by high doses of vitamin D. It is important to acknowledge that in most of these trials of vitamin D supplementation, a broad population of people were targeted, and their responses may not apply to individuals with vitamin D deficiency.

Supplementation of vitamin D

General principles of supplementation

Supplementation with ergocalciferol and cholecalciferol has been growing in the United States over the last decade, resulting in population level increases in serum 25-D levels [104,105]. The impact of supplementation on vitamin D status is somewhat mitigated by the simultaneous activation of vitamin D catabolism [16]. For instance, in studies in which ergocalciferol (vitamin D_2) is supplemented, serum levels of cholecalciferol (vitamin D_3) often fall in compensation [106]. Similar phenomena occur with supplementation of cholecalciferol that yields some reduction in serum vitamin D_2 levels, but this may be less marked than with ergocalciferol supplementation. Less potent induction of catabolism is suggested as the mechanism underlying stronger immediate effects of cholecalciferol as compared with ergocalciferol on serum total 25-D in many studies [43,107]. Calcifediol, or 25-D_3, appears to replete 25-D levels faster than the parent compound D_3 and could be considered the preferred treatment in more resistant patients [108].

Supplemental doses typically range between 400 and 4000 IU daily for disease prevention [109]. Vitamin D is a fat-soluble vitamin and is stored in adipose tissue. For this reason, repletion of vitamin D levels among patients with higher body mass index (i.e., with greater body fat) can be challenging with more modest effects of supplementation [109]. Supplementation needs may also differ for patients who have darker skin pigmentation that may suppress cutaneous 25-D production and who have less exposure to sunlight due to geographic location, institutionalization, use of sunscreen, or sun avoidance. In the United States, exposure to foods fortified with vitamin D may vary extensively according to a person's dietary patterns or preferences for nonmodified foods. Seasonal variation is also a major factor in the measurement and supplementation of vitamin D, with levels lowest in the winter and highest in late summer in many areas around the globe [88]. Care should be taken to ensure seasonal effects are considered when measuring vitamin D and considering supplementation.

At this time, vitamin D supplementation is most appropriate for patients with vitamin D deficiency. One should avoid long-term, high bolus doses of vitamin D that have been associated with poor outcomes in clinical trials. Additional risks to consider with supplemental vitamin D include hypercalcemia, nephrocalcinosis, and nephrolithiasis [6,73,100,110,111]. Supplementation in individuals without osteoporosis or clinical vitamin D deficiency is currently not recommended by the United States Preventive Services Task Force [112].

Supplementation of vitamin D in mild-to-moderate CKD

As kidney disease worsens, the capacity of the kidney to perform 1α-hydroxylation of 25-D is diminished. In clinical studies, reduction of 1α-hydroxylase activity begins early in CKD when estimated glomerular filtration rate is modestly reduced and continues to fall through the progression to end-stage kidney disease [60]. This fall is likely the result of rising levels of fibroblast growth factor-23 in kidney disease. The rise in serum fibroblast growth factor-23 acts to help control phosphorus homeostasis as glomerular filtration of phosphorus falls [113]. However, in addition to promoting phosphaturia, the increasing serum fibroblast growth factor-23 inhibits the transcription of 1α-hydroxylase, the enzyme responsible for generating active vitamin D [114]. In contrast, parathyroid hormone, the other major hormone controlling phosphorus excretion, stimulates the 1α-hydroxylase enzyme. Increased parathyroid hormone secretion counteracts the falling 1,25-D and the hypocalcemia that may result. A consequence of this homeostatic response is the development of secondary hyperparathyroidism and related bone disease. As a result of this process, abnormalities of calcium, phosphorus, parathyroid hormone, and bone histology progressively develop as kidney disease worsens [60,63,115]. For this reason, treatment of the vitamin D axis in CKD may be particularly relevant to prevent severe skeletal complications.

Joint nutritional guidelines from the National Kidney Foundation's Kidney Disease Outcomes Quality Initiative and the Academy of Nutrition and Dietetics recommend supplementation with ergocalciferol or cholecalciferol for insufficiency or deficiency in CKD with goals similar to the general population [116]. No specific guidance is provided on the screening or use of active vitamin D sterols in more advanced CKD. The Kidney Disease: Improving Global Outcomes Clinical Practice Guidelines for CKD–Mineral and Bone Disorder makes a similar recommendation but also suggests evaluating for vitamin D deficiency when parathyroid hormone levels are consistently elevated or rising in CKD. Active 1,25-D and its analogs are not suggested for patients with stage G4–G5 CKD unless there is evidence of severe and worsening hyperparathyroidism [66].

Vitamin D in prevention of kidney outcomes

Some observational studies support a potential role for vitamin D supplementation in reducing albuminuria, a major risk factor for CKD progression [57,117–121]. In uncontrolled interventions, treatment with cholecalciferol or ergocalciferol reduced proteinuria to a clinically meaningful degree [122–124]. 1,25-D has also been shown to reduce albuminuria or dipstick proteinuria in many small, short-term randomized trials [125–128], although not all studies demonstrate this effect [129]. This potential benefit may be due to modulation of the renin–angiotensin system by vitamin D [31,130]. Some observational cohort studies also support an association between lower serum vitamin D levels and loss of kidney function or development of end-stage kidney disease, a clinically more meaningful outcome [120,131–134]. Results might have been more convincing if the vitamin D assays had focused on free or bioavailable vitamin D or if variations in the gene encoding VDBP (GC) were considered [57,135]. At the time of publication the potential reno-protective effects of vitamin D remain controversial. Despite these seemingly favorable effects, studies to date have been small, and no clinical trials have clearly demonstrated beneficial effects of vitamin D on the progression of kidney disease.

Vitamin D, secondary hyperparathyroidism, and bone outcomes in mild-to-moderate CKD

Classic metabolic studies demonstrate that repletion of 1,25-D, the formation of which is impaired in CKD, can restore intestinal calcium absorption, mitigate secondary hyperparathyroidism, and improve related bone histology in patients with mild-to-moderate CKD [136–140]. More recently, treatment of vitamin D insufficiency or secondary hyperparathyroidism with vitamin D has been shown to lower parathyroid hormone in some, but not all [141], controlled and uncontrolled studies [142–144]. Metaanalyses of randomized controlled trials and observational studies confirm these benefits, although effects of 1,25-D may be stronger than for vitamin D_2 or vitamin D_3 [145,146]. Extended release formulations of calcifediol also improve 25-D and lower parathyroid hormone in short-term trials of patients with CKD and were approved for this use by the Food and Drug Administration in 2016 [147]. Whether earlier treatment to prevent secondary hyperparathyroidism in mild-to-moderate CKD can prevent major bone abnormalities and lead to a net benefit in clinical outcome needs to be studied.

Vitamin D and cardiovascular disease in mild-to-moderate CKD

Despite evidence that vitamin D supplementation can improve vitamin D status, large metaanalyses do not clearly indicate that such supplementation improves markers of cardiovascular disease in the general population. Results from these analyses were the same whether patients had sufficient or insufficient levels of vitamin D at baseline [148]. Major recent trials designed to evaluate cardiovascular disease also did not demonstrate the benefits of supplementation [93,94,149]. Notably, these studies primarily focused on the general population, and results could be different in CKD due to the altered vitamin D physiology.

In CKD, small trials largely show conflicting results on the effects of vitamin D or 1,25-D supplementation on surrogate cardiovascular outcomes, such as vascular stiffness, endothelial function, or cardiac remodeling. In 87 patients with CKD, treatment with either calcitriol or calcifediol for 6 months resulted in modestly reduced aortic pulse wave velocity, a marker of stiffness [129]. However, in another study of CKD patients, supplementation with 2000 IU daily of cholecalciferol or 0.5 μg daily of calcitriol for 6 months did not improve pulse wave velocity in CKD [141]. In contrast, in an additional study of 120 patients with CKD and vitamin D deficiency, supplementation with cholecalciferol for 16 weeks improved vascular function as indicated by increased flow-mediated dilation and reduction in pulse wave velocity [150]. Other small studies also demonstrate improved flow-mediated dilation after 1,25-D [151,152]. Studies of cardiac geometry have been disappointing, showing no improvement in left ventricular mass or geometry in patients with CKD treated with 1,25-D [153,154]. Altogether these studies are limited by small sample sizes and reliance on surrogate outcomes. Larger studies and those focused on clinical outcomes are needed to determine if supplementation with vitamin D in mild-to-moderate CKD can improve cardiovascular outcomes, perhaps via effects on endothelial function or vascular stiffness.

Formulations of vitamin D in CKD

Limited data are available on the optimal formulations and dosing for treatment of vitamin D deficiency in CKD. A variety of vitamin D regimens have been studied in clinical trials of patients with CKD and found to be safe and effective in studies of modest duration (Table 25.3) [106,142,155,157]. One small, short-term clinical trial demonstrated a more robust response to supplementation with cholecalciferol (D_3) compared with ergocalciferol (D_2) using comparable doses; however, vitamin D status was similar among the treatment groups 4 weeks after supplementation [155]. No studies are available demonstrating an optimal regimen or dosing for long-term vitamin D status.

TABLE 25.3 Selected nutritional vitamin D formulations and regimens used in interventional studies for adult patients with mild-to-moderate chronic kidney disease.

Formulation	Dose	Duration
Cholecalciferol	50,000 IUs/week	8–12 weeks with or without maintenance [16,142,155,156]
Cholecalciferol plus calcium	800 IU and 1200 mg daily	24 months [157]
Cholecalciferol	2000 IU daily	6 months [141]
Cholecalciferol	40,000 IU weekly	8 weeks [144]
Cholecalciferol	50,000 IUs/month	3 months [158]
Cholecalciferol	4000 IUs daily for 1 month, followed by 2000 IU daily	3 months [159]
Cholecalciferol	2000 IUs daily versus 40,000 IUs monthly	6 months [160]
Ergocalciferol	50,000 IUs/week	12 weeks [155]
Ergocalciferol	50,000 IUs twice weekly	5 weeks [106]
Ergocalciferol	40,000 IUs/week	12 weeks [123]

Vitamin D supplementation in special CKD populations

Vitamin D supplementation in diabetic kidney disease

Patients with diabetes and kidney disease may be an important population for vitamin D monitoring or supplementation. Diabetic kidney disease is accelerated by activation of the renin–angiotensin–aldosterone system. Due to the role of vitamin D deficiency in activating these pathways, maintaining vitamin D function may be more important in this group [57,134]. Randomized controlled trials demonstrate albuminuria reduction with 1,25-D supplementation in diabetic kidney disease [128]. Small uncontrolled studies suggest that nutritional vitamin D (i.e., vitamin D_2 and vitamin D_3) may also convey this benefit, but most of the studies are short term [124,161]. Longer term trials of vitamin D and 1,25-D supplementation evaluate the impact on more clinical kidney outcomes.

Vitamin D supplementation in nephrotic syndrome

Vitamin D circulates bound to albumin and VDBP, both of which partially cross the normal glomerular filtration barrier in the kidney. Vitamin D, in complex with VDBP, is reabsorbed in the proximal tubule as discussed in detail in Section 1.1. However, in the nephrotic syndrome, the glomerular barrier is disrupted, leading to a marked increase in flux of many serum proteins into the urine, including VDBP and albumin. The capacity of the proximal tubule to reabsorb increased albumin and VDBP is overwhelmed and large amounts of vitamin D are lost in the urine. Vitamin D deficiency has been noted in patients with the nephrotic syndrome for over 4 decades [162–164]. In severe cases, osteomalacia and hypocalcemia are evident [115]. Lower 25D levels also contribute to secondary hyperparathyroidism [165]. Despite wasting of VDBP and vitamin D in the urine, supplementation with vitamin D can improve deficiency based on longitudinal observations [164].

Vitamin D supplementation in advanced CKD and end-stage kidney disease

In end-stage kidney disease, due to deficits in 1α-hydroxylase activity that are driven by rising fibroblast growth factor-23 and renal scarring, it is likely that repletion of 25-D stores may not correct 1,25-D deficiency. Despite this concern, treatment with nutritional vitamin D in patients with end-stage kidney disease on dialysis has been studied because of the potential peripheral conversion to 1,25-D or direct effects of 25-D itself. In several trials and observational evaluations, including patients with end-stage kidney disease on dialysis, nutritional vitamin D can raise circulating 25-D [32,166–170]. Nutritional vitamin D may contribute to an increase in serum 1,25-D and lowering or stabilization of parathyroid hormone in some [167,171–173], but not all, studies [168–170]. Thus far, however, these changes have not translated into clinical improvement in vascular function, physical functioning, quality of life, or other important outcomes [32,168,169].

Supplementation with 1,25-D and other active vitamin D sterols is a major feature of therapy for abnormal bone and mineral metabolism in advanced CKD and end-stage kidney disease. 1,25-D sterols can lower parathyroid hormone levels toward normal and prevent severe bone complications [5,66,174,175]. The effects on other outcomes such as cardiovascular disease and mortality have not been proven in clinical trials.

After kidney transplantation the stimulus for fibroblast growth factor-23 production is reduced, and 1,25-D levels can again rise. However, after years of parathyroid overstimulation, irrepressible hyperplasia of the gland may have developed, and parathyroid hormone may not fully normalize despite restoration of normal 1,25-D, a state often termed “tertiary hyperparathyroidism” [176]. Practitioners prescribing 25-D and active vitamin D sterols in the posttransplant setting must be aware of changes in the vitamin D–parathyroid hormone axis in their patients to avoid hypercalcemia and hypophosphatemia as a result of tertiary hyperparathyroidism.

Vitamin D supplementation in pediatric kidney disease

In children with CKD, additional consideration must be given to the growing skeleton. Vitamin D deficiency and resulting secondary hyperparathyroidism in children can lead to abnormal bone mineralization and high bone turnover disease similar to adults. In children, vitamin D deficiency also causes abnormalities in the growth plate that also result in growth restriction and deformity, a condition known as rickets [24,25]. The effects of vitamin D on the bone and mineral hormonal axis, including parathyroid hormone, and the risk factors for vitamin D deficiency appear similar in children and adults [165,177]. Few large, well-conducted studies are available in children with CKD to differentiate management as compared with adults, and recommendations for supplementation and treatment are similar to the management in adults [66,178].

Potential benefits with regard to treatment and prevention of secondary hyperparathyroidism are probably similar in children and adults [177,179]. For nonskeletal outcomes, such as kidney disease progression or albuminuria, associations appear similar in children and adults although there is no support for these effects yet from clinical trials [120].

Current controversies and summary recommendations

There is still no agreement on target levels and optimal intake of vitamin D in the general adult population. Observational studies and clinical trials have evaluated different populations and end points making a meaningful compilation of results challenging. Overall, few studies have definitively demonstrated nonskeletal benefits of vitamin D supplementation. Benefits of modest-to-moderate doses of vitamin D supplementation on bone may only accrue to those with documented deficiency or insufficiency and in cases where large boluses of vitamin D are not given. The United States Preventive Services Task Force currently cites insufficient evidence to support vitamin D screening or supplementation for asymptomatic adults in the United States [112,180]. How to apply these recommendations to patients with kidney disease is unclear.

In kidney disease, unique considerations include the increased risk of 25-D deficiency among those with heavy proteinuria and the inadequate metabolism of 25-D to 1,25-D resulting in secondary hyperparathyroidism. In the context of CKD stages 1–5, treatment of 25-D deficiency may help lower elevated serum parathyroid hormone, but the long-term effects on prevention of refractory hyperparathyroidism or kidney-related bone disease is not well established. In end-stage kidney disease, treatment with 1,25-D compounds can control secondary hyperparathyroidism and prevent severe skeletal abnormalities, but there are also dose-limiting toxicities such as hypercalcemia and vascular calcification. Few studies are available that have examined the effects of 1,25-D compounds on such clinical outcomes as fracture, cardiovascular disease or mortality in CKD patients. With alternative agents, such as calcimimetics, available to control secondary hyperparathyroidism in end-stage kidney disease, more studies of 1,25-D are needed.

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C H A P T E R

26

Vitamin metabolism and requirements in chronic kidney disease and kidney failure

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Chronic kidney disease (CKD) commonly alters the biochemistry, metabolism, and nutritional requirements for many vitamins and enhances the likelihood of abnormal vitamin function. Both deficiencies and abnormally high levels of vitamins may occur in patients with renal failure. These abnormalities are reviewed in this chapter. Since the last edition of this book, new research has emerged regarding, among other matters, vitamin intake, interference of phosphate binders with intestinal vitamin absorption, vitamin K status in CKD, and the use of vitamins in critically ill patients. Moreover, the recent KDOQI Clinical Practice Guidelines (CPGs) for nutrition in CKD address vitamin supplementation for CKD 3−5D patients [1]. These guidelines are addressed in this chapter. Vitamin D nutrition is reviewed elsewhere (Chapter 23: Calcium, Phosphate, PTH, Vitamin D and FGF-23 in CKD-Mineral and Bone Disorder, and Chapter 25: Vitamin D in Kidney Disease) and will not be addressed in this chapter, and vitamin needs in patients with acute kidney injury (AKI) are also discussed in Chapter 35, Metabolic Management and Nutritional Support in Acute Kidney Injury.

Note: Some terms in this chapter regarding the dietary needs of a nutrient are defined as follows: the recommended dietary allowance or recommended daily allowance (RDA) refers to the average daily dietary intake of an essential nutrient that is sufficient to meet the requirement for that nutrient in nearly all (97%−98%) of healthy individuals of a given life stage and gender [2]. When the RDA cannot be determined, an "adequate intake" (AI) may be used. The AI refers to the recommended average daily intake level that is assumed to be adequate and which is based on observed or experimentally determined approximations or estimates of the nutrient intake by a group or groups of apparently healthy people. RDA and AI are mainly used in the United States. The estimated average requirement (EAR) is the average daily nutrient level estimated to meet the requirements of half the healthy individuals in a given life stage and gender group. It is usually used in Europe [3,4]. Some papers refer to the recommended dietary intake (RDI) or dietary reference intake (DRI) from local guidelines without being more precise or specific.

Vitamin A, physiology, biochemistry, and nutritional status in chronic kidney disease patients

Vitamin A physiology and biochemistry

Vitamin A is composed of several compounds, including retinol and the biologically active retinoids, which have a common structure consisting of four isoprenoid units (20 carbons) with five double bonds (Table 26.1) [5]. Retinol, retinoic acid, and retinal are the main bioactive retinoic compounds. Since the 1990s, the accepted units for the quantification of vitamin A have changed from international units (IUs) to retinol equivalents (REs), where 1.0 IU = 0.3 μg RE [6]. Carotenoids, which are 40-carbon compounds, may

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TABLE 26.1 Physicochemical and clinical characteristics of vitamins.

Vitamin	Main compound	Solubility	MW	Protein binding in plasma	HD losses	Peritoneal losses	Body stores	Toxicity[a]
A	Retino	Lipid	286	RBP + prealbumin	None	Controversial[b]	Large	Yes
E	α-Tocopherol	Lipid	431	Lipoproteins	None	Small	Small	Possible
K	Phylloquinone (K1)	Lipid	451	Lipoproteins	NA[c]	NA[c]	Small	No
B1	Thiamine	Water	337	Albumin	13–40 mL/min[d]	Low	4–10 days	No
B2	Riboflavin	Water	376	Weak albumin, IgG	27–52 mL/min[d]	High	2–3 months	No
B6	Pyridoxine	Water	169	Albumin	54 mL/min[e]	= or <urinary excretion	3–4 months	Yes
B12	Cyanocobalamin	Water	1355	Transcobalamin II	Controversial[f]	None	Years	NA[c]
C	Ascorbic acid	Water	176	No	80–280 mg/session[d]	40–56 mg/day	3–4 months	Yes
Folates	Pteroylglutamic acid	Water	441	No	135 mL/min[e]	1/3 of RDA	>1 year	Yes
Niacin	Nicotinic acid	Water	123	Weak	Very low	NA[c]	2 months	NA[c]
Biotin	Biotin	Water	244	Weak	52 mL/min[d]	NA[c]	50 weeks	None
Pantothenic acid	Pantothenic acid	Water	219	NA[c]	30 mL/min[d]	NA[c]	Several weeks	None

[a] *For normal individuals.*
[b] *See the section on vitamin A.*
[c] *Not available.*
[d] *Values obtained with low-flux/low-efficiency dialysis.*
[e] *Values obtained with high-flux/high-efficiency dialysis.*
[f] *Possible effects of convective forces.*
HD, Hemodialysis; *MW*, molecular weight; *RBP*, retinol-binding protein.

be biologically active and are vitamin A precursors. Variable quantities of carotenoids are converted to retinol; this conversion is regulated according to the body vitamin A levels [7]. The allo-*trans*-β carotene is the main bioactive carotenoid. Retinoids and carotenoids are fat soluble and are predominantly found in foods derived from animals for the retinyl esters and from vegetables for the carotenoids [8]. During digestion, retinyl esters are hydrolyzed in the intestinal lumen by pancreatic lipase. Retinol and carotenoids are incorporated into micelles and absorbed by enterocytes, where β-carotene is converted to retinol. Retinol is esterified, combined in chylomicrons, and broken down into chylomicron remnants in the lymphatic system by lipoprotein lipase. Hepatic cells incorporate the chylomicron remnants through apolipoprotein (apo)-E or B receptors. A significant part (10%–40%) of the absorbed retinoids are oxidized or conjugated and excreted into bile and urine.

At least 50% of the retinoid compounds are transferred into the perisinusoidal stellate cells of the liver where they are stored as retinyl palmitate and other retinyl esters. In plasma, retinol is largely bound to apo-retinol-binding protein (RBP-4), a 21.3-kDa protein primarily synthesized in the liver and adipose tissue. This equimolar complex is bound to prealbumin (also called transthyretin) and delivered to the target where it binds to RBP cell-surface receptors. Retinol is incorporated into the cell, whereas the carrier protein, apo-RBP, is released and catabolized by the kidney. At the cellular level the active form of vitamin A is all-*trans*-retinoic acid, synthesis of which is tightly regulated [9]. The physiological effects of vitamin A are mediated through the retinoic acid nuclear receptors and retinoid X receptors, which belong to the same nuclear receptor superfamily as the vitamin D receptor. Several medications may interfere with vitamin A metabolism or actions. These are summarized in Table 26.2. Plasma vitamin A is usually measured by high-pressure liquid chromatography (HPLC), which has replaced older colorimetric methods. Vitamin A is necessary for normal nocturnal vision; it plays a role in the immune response, in the differentiation of epithelial cells, and the morphogenesis of solid organs, including the kidney, and it has antioxidant properties [10,11]. Because 13-*cis*-retinoic acid promotes cellular differentiation, it has been used to treat acute promyelocytic leukemia [12]. Large-scale clinical trials failed to demonstrate a benefit of large doses of retinol and carotenoids for the prevention of cancer or cardiovascular (CV) disease [13]. An increased death rate was actually reported in patients given vitamin A supplements, which may be attributed to the prooxidant effects of carotenoids [7].

TABLE 26.2 Medicines and other substances that may interfere with vitamin metabolism and may contribute to vitamin deficiency.

Interactions of vitamins with drugs		
Vitamin	**Interacting medication**	**Effect of interaction**
Vitamin A	Tetracyclines	Risk of intracranial hypertension
	Antacids	Increase of their efficacy
	Anticoagulants	Risk of bleeding
	Bile acid sequestrants	Reduces intestinal vitamin A absorption
	Statins	Increase vitamin A levels in the blood
	Doxorubicin	Vitamin A enhances its action
	Orlistat	Reduces intestinal vitamin A absorption
	Retinoids	Toxicity (nausea, vomiting, blurred vision, etc.)
Vitamin E	Cyclosporine	Vitamin E increases intestinal cyclosporine absorption
	CYP3A4 substrates	Vitamin E reduces their effectiveness through acceleration of their breakdown
	Anticoagulants/antiplatelets	Vitamin E enhances their effects
	Statins	Vitamin E decreases their effectiveness
Vitamin K	Cephalosporins, sevelamer	Reduces the intestinal absorption of vitamin K
	Phenytoin	Interferes with the metabolism of vitamin K
	Warfarin	Its activity is antagonized by vitamin K
Vitamin B1 (thiamine)	Phenytoin, penicillins, cephalosporins, aminoglycosides, tetracycline derivatives, loop diuretics, fluoroquinolones, sulfonamide derivatives, trimethoprim	Long-term use may deplete thiamine
Vitamin B6 (pyridoxine HCl)	Levodopa	Decreases effectiveness of levodopa; increases Parkinsonian symptoms
	Phenytoin	Increases risk of seizures
	Isoniazid, penicillamine, cycloserine, ethionamide, and theophylline	Blocks synthesis of pyridoxine-L-phosphate
Folic acid	Methotrexate	Folic acid supplementation reduces toxicity without affecting efficacy
	Antacids, H2 blockers, proton pump inhibitors, bile acid sequestrants, carbamazepine, NSAIDs, sulfasalazine, and triamterene	Decrease folate intestinal absorption
Vitamin B12	Anticonvulsants, chemotherapy medications, colchicine, bile acid sequestrants, H2 blockers, metformin, and proton pump inhibitors	Reduces B12 levels
Vitamin C (ascorbic acid)	Aspirin/NSAIDs	Increases urinary excretion of vitamin C
		Vitamin C increases the drug blood levels
	Acetaminophen	High vitamin C doses reduce urine excretion
	Aluminum-containing antacids	Vitamin C increases aluminum absorption
	Barbiturates	Decrease the effects of vitamin C by increasing its urinary excretion
	Chemotherapy drugs	Vitamin C interferes with chemotherapy agents
	Nitrates	Vitamin C reduces tolerance to nitrates
	Oral contraceptives/hormone replacement therapy	Vitamin C raises estrogen levels
	Protease inhibitors	Vitamin C lowers plasma levels of protease inhibitors

(*Continued*)

TABLE 26.2 (Continued)

Interactions of vitamins with drugs		
Vitamin	**Interacting medication**	**Effect of interaction**
Vitamin B2 (riboflavin)	Anticholinergic drugs	Anticholinergic drugs inhibit intestinal absorption of riboflavin
	Tetracycline	Riboflavin reduces intestinal absorption and effectiveness of tetracyclines
	Doxorubicin	Riboflavin deactivates and is depleted by doxorubicin. (Is this what you mean?)
	Tricyclic antidepressants, phenothiazines	These compounds inhibit riboflavin's actions
	Phenytoin, methotrexate	
	Probenecid	Decreases the absorption of riboflavin from the gastrointestinal tract and decreases the urine riboflavin excretion
	Thiazide diuretics	Increase urine riboflavin excretion
Niacin/nicotinamide	Statins	Statins increase the risk of myopathy and rhabdomyolysis
Biotin	Antibiotics	Antibiotics reduce the intestinal microflora that produces biotin
	Anticonvulsants	Carbamazepine and phenytoin reduce biotin levels
Pantothenic acid (vitamin B5)	Tetracycline	Pantothenic acid interferes with intestinal absorption and effectiveness of tetracyclines
	Cholinesterase inhibitors	Pantothenic acid may increase the effects of cholinesterase inhibitors

CYP3A4, Cytochrome P450 3A4; *NSAIDs*, nonsteroidal antiinflammatory drugs.
Modified from Kosmadakis G, Da Costa Correia E, Carceles O, Somda F, Aguilera D. Vitamins in dialysis: who, when and how much?. Ren Fail 2014;36:638–50, with permission.

Vitamin A intake in chronic kidney disease patients

Data regarding vitamin A intake in patients with advanced CKD and dialysis patients are conflicting. No data are currently available concerning desirable vitamin A intake for nephrotic patients. Interestingly, regarding the incidence of CKD in a large cohort of healthy subjects with normal glomerular filtration rate (GFR), the upper quintiles of vitamin A intake were not associated with a significantly lower incidence of CKD during follow-up [14]; this is in opposition to the findings regarding the upper quintiles of folate and vitamins B12, C, and E. Vitamin A intake with the protein-restricted diets usually prescribed to nondialyzed CKD patients is reported in Table 26.3 from Stein et al. [15]. These investigators reported that the vitamin A intake with protein-restricted diets is slightly below the RDA. In 210 nondialyzed CKD patients (mean GFR, 17.1 ± 6.5 mL/min), Chan et al. [16] reported an adequate vitamin A intake; however, the protein intake was large, 1.18-g protein/kg body weight/d. A more recent study addressed micronutrient intake in CKD, maintenance hemodialysis (MHD), chronic peritoneal dialysis (CPD) patients, and kidney transplant recipients who were not receiving vitamin supplements [4]. Vitamin A intake was found, respectively, to be 38%, 75%, 52%, and 55% of the EAR. Bossola et al. [3] obtained 3-day diet diaries in 128 MHD Italian patients and reported the vitamin A intake to be below the Italian RDI in 94.6% of the patients. In 242 continuous ambulatory peritoneal dialysis (CAPD) patients, Wang et al. [17] reported adequate vitamin A intakes, regardless of the adequacy of dialysis and of the residual renal function (RRF) of the patients. In contrast, Martin-Del-Campo et al. [18] reported vitamin A intake to be below the DRI in 40% of 73 CPD patients, independent of their nutritional status. Vitamin A intake was even lower in those patients [18] who had a serum C-reactive protein (CRP) greater than 12.2 mg/L. The lower vitamin A intake in this latter study was attributed to the specific characteristics of Mexican food. In summary, in many but not all studies of vitamin A intake in CKD 3–5D and kidney transplant patients, vitamin A intake was not uncommonly below the RDA.

Vitamin A nutritional status in chronic kidney disease, chronic dialysis, acute kidney injury, and kidney transplant patients

Abnormally high plasma vitamin A levels and an increased rise in plasma vitamin A in response to a

TABLE 26.3 Typical vitamin contents of different diets prescribed to chronic renal failure patients[a].

Dietary protein intake	Vitamin A (μg RE[b])	Vitamin E (mg)	Vitamin K (μg)	Thiamine (mg)	Riboflavin (mg)	Biotin (μg)	Pyridoxine (mg)	Folic acid (μg)	Vitamin B12 (μg)	Niacin (mg)	Ascorbic acid (mg)	Pantothenic acid (mg)
40 g	556	16.0	80	1.2	0.8	13.4	1.4	50	0.6	9.0	107	3.0
60 g	570	12.0	80	1.5	1.4	17.8	1.5	80	1.2	10.5	88	4.0
80 g	568	14.0	80	1.3	1.2	15.8	1.8	70	2.5	15.0	60	3.2
RDA[c]	700–900	15	80–120	1.1–1.2	1.1–1.3	30[d]	1.3–1.7[e]	400	2.4	14–16	75–90[f]	5[d]

[a] *Data calculated from food tables and referring to 24-h intake of the nutrient from the diet.*

[b] *RE: Retinol equivalents.*

[c] *RDA: Recommended dietary allowance for healthy, nonpregnant, nonlactating adults.*

[d] *This value is not an RDA; there is inadequate scientific evidence to allow the calculation of RDA. Recommended intake, termed "adequate intake" is used instead. It is derived from experimental data or by an approximation of observed mean intakes, as suggested by the Standing Committee on the Scientific Evaluation of Dietary Reference Intakes [348].*

[e] *In female and male adults below the age of 50, the RDA is 1.3 mg/d. Over the age of 50 the RDA is respectively 1.5 and 1.7 mg/d for women and men.*

[f] *Values of the RDA are for nonsmoking female and male adults. Add 35 mg/d for smokers [48].*

From Stein G, Sperschneider H, Koppe S. Vitamin levels in chronic renal failure and need for supplementation. Blood Purif 1985;3:52–62.

vitamin A load were reported in CKD patients as long ago as 1945 [19]. Investigators have consistently found elevated plasma concentrations of total vitamin A, RBP-bound vitamin A, and free vitamin A in nondialyzed CKD patients and maintenance dialysis patients, including children [15,20–25]. In patients with the nephrotic syndrome, plasma RBP, retinol, and retinyl esters levels have also reported to be increased [26], even in the absence of renal failure. Recently, Bataille et al. [27] found that 91.9% of 123 MHD patients had high plasma retinol concentrations. Increased plasma vitamin A in CKD is classically attributed to altered RBP and RBP–retinol metabolism. After the delivery of retinol to target tissues, free RBP can be filtered by the glomerulus and catabolized by renal tubule cells. Thus in renal failure, RBP catabolism is impaired, resulting in increased plasma RBP and plasma RBP/prealbumin and RBP/retinol ratios [28]. Also, the small proportion (5%) of the RBP–retinol complex that is not bound to transthyretin is filtered at the glomerulus. This complex is captured by the proximal tubular cells by a specific apical receptor, megalin, which allows for retinol recycling into the blood stream at the basolateral level of the cell. Knockout mice for megalin display a urinary loss of the RBP–retinol complex [29]. Thus the loss of GFR in kidney failure contributes to the elevated vitamin A plasma levels. However, the renal clearance of RBP-4 has recently been found to be independent of the GFR in patients with various stages of CKD (Fig. 26.1) [30], and these investigators hypothesize that the increase in plasma retinol and RBP-4 may be more of hepatic origin than related to decreased removal of RBP-4 by the kidney.

As shown many years ago, hemodialysis (HD) treatment does not change vitamin A levels [21]; indeed, substantial losses of vitamin A into dialysate would not be expected because of the relatively large size of the vitamin A–RBP–prealbumin complex. However, serum β-carotene, ubiquinol, and lycopene have been found to be lower in MHD patients than in controls [23,31], and serum β-carotene and ubiquinol fall further after a single HD session. There are no published data on the dialysis kinetics of vitamin A and RBP handling in MHD patients treated with convective techniques and daily dialysis. Data are conflicting as to whether vitamin A and RBP are present in the effluent peritoneal dialysate [22,32].

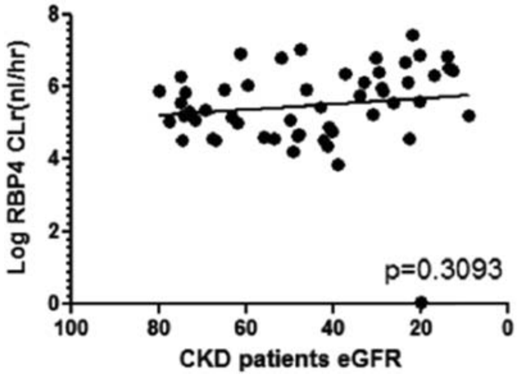

FIGURE 26.1 The absence of relationship between eGFR and renal clearance of retinol-binding protein-4. *eGFR*, Estimated glomerular filtration rate. *Source: By Jing J, Isoherranen N, Robinson-Cohen C, Petrie I, Kestenbaum BR, Yeung CK. Chronic kidney disease alters vitamin A homeostasis via effects on hepatic RBP4 protein expression and metabolic enzymes. Clin Transl Sci 2016;9:207–15, with permission.*

In patients with AKI, serum vitamin A levels were found to be normal in one study [28], decreased in another study (with normal serum RBP levels) [33], and increased in a third study of AKI patients receiving total parenteral nutrition (TPN) containing standard retinol supplementation [34]. In 40 patients treated with continuous veno-venous HD (CVVHD), Datzmann et al. [35] did not detect vitamin A in the spent dialysate. Plasma vitamin A levels decrease slowly toward normal after renal transplantation. Yatzidis and coworkers reported that more than 20 months may elapse in patients with a well-functioning kidney transplant before plasma vitamin A levels are normal [36].

Clinical effects of altered vitamin A nutrition

Potential risk of vitamin A toxicity

Whether there is an increased risk of vitamin A toxicity in nondialyzed CKD patients and chronic dialysis patients is controversial [37]. Many CKD patients who have increased plasma vitamin A levels (up to three to four times normal) do not show evidence for toxicity [38,39]. Elevated plasma vitamin A in CKD is considered by many authors to be relative, due to the protective effects of increased plasma RBP, and to have no clinical significance, if the vitamin A/RBP ratio is normal or low. Vitamin A toxicity is believed to occur when plasma retinyl esters in the lipoprotein fractions increase [11,28]. Whether vitamin A accumulates in solid tissues in CKD patients is also controversial [20,39–41]. Therefore it is not known whether the increased plasma vitamin A levels that are commonly found in CKD and chronic dialysis patients are hazardous. In patients without CKD who have vitamin A overload and toxicity, large amounts of vitamin A may accumulate in the liver. The clinical signs of vitamin A intoxication, cutaneous lesions (fissures, dryness, desquamation, and yellowish appearance), headaches and central nervous system manifestations, joint pains, bone tenderness to palpation, anemia, hepatomegaly, and muscle stiffness [11], are not specific indicators for vitamin A toxicity. Hence, these signs, when present, are not necessarily due to vitamin A toxicity.

Vitamin A and hypercalcemia

Intriguingly, in CKD patients who did not have other evidence for vitamin A toxicity, a correlation between plasma vitamin A concentrations and serum calcium levels has been reported [42]. The bone reabsorptive effects of excess vitamin A have been known for many years, and there is a report of hypercalcemia with elevated serum vitamin A levels in CKD patients as long ago as 1971 [43]. MHD patients who were taking modest doses of vitamin A supplements, 2500–15,000 IU/d, had higher serum vitamin A and calcium concentrations than those who were not. The association between elevated plasma retinol and hypercalcemia has also been found in children with CKD as early as stage 2 as well as in children undergoing dialysis therapy [44]. However, such correlations between elevated plasma vitamin A and increased serum calcium or serum alkaline phosphatase have not been consistently found. The mechanism of hypercalcemia with vitamin A toxicity is related to the osteolytic action of the retinoids on bone. Vitamin A toxicity should be considered in the differential diagnosis of hypercalcemia in CKD patients.

Vitamin A and outcomes

The prognostic value of plasma vitamin A levels in MHD and renal transplant patients has been previously analyzed. In a post hoc analysis of the 4D study in which the participants in the study were prevalent diabetic MHD patients, Espe et al. [45] found that the participants who were in the lower quartiles of plasma retinol (Fig. 26.2) and RBP-4 concentrations displayed an increased risk of sudden death, infection-related death, and overall mortality. Interestingly, the lower quartile of plasma retinol in these patients remained above the normal range of plasma retinol. These results confirm previous data reported in a smaller cohort of MHD patients [46]. One possible interpretation is that the lower plasma retinol levels are an indirect marker of inflammation. This is consistent with data from CPD patients by Martin-Del-Campo et al., mentioned earlier [18], who found a significantly lower vitamin A intake in the patients whose serum CRPs were in the highest quartile. Another hypothesis is that retinol behaves as a nutritional surrogate since its metabolism is closely associated with that of transthyretin. Bataille et al. [27] confirmed a higher mortality in MHD patients who were in the lowest plasma retinol quartile, but the significance disappeared when transthyretin was introduced in the statistical model. Also, in renal transplant recipients, as in MHD patients, decreased survival has been observed in patients in the lower tertile for plasma retinol [47]. In contrast, in the same study, plasma vitamin E and a variety of carotenoids, including β-carotene, were not associated with patient survival.

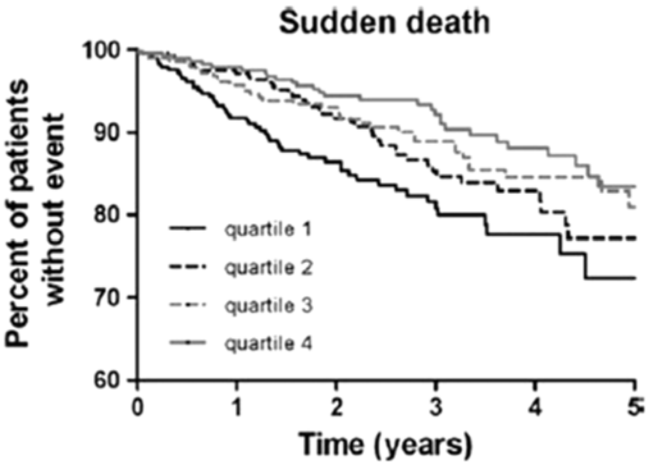

FIGURE 26.2 Relationship between plasma vitamin A plasma levels and sudden cardiac death in maintenance hemodialysis patients. Quartile 1 includes patients with the lowest plasma retinol levels as assessed by HPLC. *HPLC*, High-pressure liquid chromatography. *Source: Espe KM, Raila J, Henze A, Krane V, Schweigert FJ, Hocher B, et al. Impact of vitamin A on clinical outcomes in haemodialysis patients. Nephrol Dial Transplant 2011;26. Reproduced with permission from the Editor.*

Vitamin A supplementation in chronic kidney disease, chronic dialysis, and transplant patients

Plasma vitamin A levels in advanced CKD and chronic dialysis patients (CKD 3–5D) are elevated, and vitamin A deficiency has rarely been observed. However, even relatively small supplements of vitamin A (i.e., 2500–15,000 IU, 750–4500 μg of REs) may cause vitamin A toxicity. There is a consensus that vitamin A supplements in doses larger than the recommended daily allowance (RDA) for normal healthy adults (i.e., 700–900 μg of RE, or 2300–3000 IU [48]) should not be given to normal adults, and the same recommendation is made for CKD, MHD, CPD, and kidney transplant patients. The recommendations in the KDOQI CPGs for nutrition in CKD are consistent with the RDA [1]. However, findings from three studies demonstrate that, among MHD patients, those individuals with the lowest plasma retinol levels (but which, on average, were still above normal concentrations) have increased mortality [27,45,46]. Patients with nephrotic range proteinuria excrete substantial amounts of vitamins that are bound to protein. Hence, a daily intake of the RDA for vitamin A is recommended for nephrotic individuals. For renal transplant recipients, vitamin A supplements do not appear necessary unless their vitamin A intake is low. Vitamin A supplements are probably not necessary for AKI patients unless they are nourished by TPN for at least 2 weeks. Given the risks of vitamin A toxicity in advanced CKD patients and reports of vitamin A toxicity in TPN patients with AKI receiving as little as 1500 μg of RE (5000 IU)/d [34], it is recommended that no more than the RDA for vitamin A (700–900 μg/d or—2300–3000 IU/d—for nonpregnant, nonlactating adults) should be given for AKI patients receiving TPN as their sole nutritional source (Table 26.4).

Summary:

- Serum vitamin A is frequently increased in advanced CKD, MHD, and CPD patients, even though vitamin A intake is usually decreased.
- The mechanism for this increase has been attributed to decreased catabolism of RBP-4, but recent data suggest that enhanced hepatic synthesis may contribute to this elevation.
- There is no obvious toxicity that has been associated with the typical increase in plasma vitamin A levels found in advanced CKD and chronic dialysis patients.
- However, hypercalcemia may be associated with high plasma retinol levels.

Continued

- The lower quintiles of plasma retinol levels, even if still above normal values, are associated with increased mortality in MHD patients and renal transplant recipients. Inflammation and poor nutritional status may have a causal role in this relationship.
- There is no evidence suggesting that vitamin A should be routinely supplemented for advanced CKD, chronic dialysis, or kidney transplant patients. This position is consistent with the KDOQI CPGs on nutrition in CKD.

Vitamin E, physiology, biochemistry, and nutritional status in chronic kidney disease patients

Vitamin E physiology and biochemistry

Vitamin E is a fat-soluble vitamin for which the main active compound is α-tocopherol (Table 26.1); there are other naturally occurring isomers of vitamin E (β, γ, δ) as well. A genetic deficit of the α-tocopherol transfer protein provokes a severe neurologic disorder that occurs between the ages of 5 and 15 years and is called AVED (ataxia with vitamin E deficiency), also referred to as Friedreich-like ataxia. It is associated with a markedly reduced serum α-tocopherol level. Only supplementation with α-tocopherol can improve the clinical burden of this disease; the other isoforms of tocopherol are ineffective. Based on this fact, Azzi recently disputed the appellation of "vitamin" for the other isoforms of tocopherol [49].

The main sources of vitamin E are vegetable oils, such as corn, soybean, wheat germ, and sunflower oil [50]. Animal products are not rich sources of vitamin E. Vitamin E metabolism has recently been extensively reviewed [51]. After intestinal absorption of vitamin E congeners, these compounds are transported with fat, mainly through the lymphatic flow, into the venous circulation [52]. In plasma, there is no specific carrier for α-tocopherol. It is transported in plasma by lipoproteins, and its plasma concentration is affected by the lipid content of blood. Assessment of the nutritional status of vitamin E is difficult. HPLC has been widely used for decades to measure serum vitamin E levels [53,54]. The cell membrane concentrations of α-tocopherol and/or its antioxidant activity may give more helpful information concerning the adequacy and activity of tissue α-tocopherol levels than plasma α-tocopherol concentrations. Vitamin E is the main antioxidant in biological membranes and protects phospholipid membranes from oxidative stress. Vitamin E deficiency due to intestinal malabsorption has been reported to increase hemolysis by causing membrane fragility [53]. Vitamin E also has antiinflammatory properties, including, among others, regulation of protein kinase C, PPAR-γ, and NF-κB, that has antiatherogenic

TABLE 26.4 Recommendations/suggestions for daily vitamin supplementation for chronic kidney disease (CKD), maintenance hemodialysis (MHD), and chronic peritoneal dialysis (CPD) patients.

	RDA[a] in healthy adult subjects	Nephrotic syndrome	Nondialysis CKD patients	Nondialysis CKD patients	Nondialysis CKD patients	MHD patients	MHD patients	MHD patients	CPD patients
Origin	Dietary reference intake [48,348,361]	Authors suggestions	CARI [357][b]	Steiber and Kopple [358][c]	KDOQI guidelines [1]	EBPG [86]	KDOQI guidelines [1]	Author suggestions	Author suggestions
Vitamin A	700–900 RE[d]	Up to RDA[e]	None	Up to the RDA[e]	None	None	None	None[f]	None
Vitamin E	22.5 IU	Up to RDA[e]	No suggestion	Up to the RDA[e]	None	400–800 IU	None	Up to the RDA[e]	400–800 IU
Vitamin K	80–120 μg	None	No suggestion	Supplements of antibiotherapy	None[g]	None[h]	None[h]	None[h]	None[h]
Vitamin B1	1.1–1.2 mg	Unknown[i]	>1 mg	1.1–1.2 mg	Not specified	1.1–1.2 mg	Up to the RDA[e]	1.1–1.2 mg	1.1–1.2 mg
Riboflavin	1.1–1.3 mg	Unknown	1–2 mg		Not specified	1.1–1.3 mg	Up to the RDA[e]	1.1–1.3 mg	1.1–1.3 mg
Vitamin B6	1.3–1.7 mg	5 mg[j]	1.5–2 mg	5 mg[j]	Not specified	10 mg[j]	Up to the RDA[e]	10 mg[j]	5 mg [j]
Vitamin C	75–90 mg	75–90 mg	Up to 60 mg	30–60 mg	75–90 mg	75–90 mg	75–90 mg	75–90 mg	75–90 mg
Folic acid	400 μg	Unknown	200 μg in the case of EPO therapy	Up to the RDA[e]	If clinical signs and symptoms	1 mg	If clinical signs and symptoms	1 mg	1 mg
Vitamin B12	2.4 μg	RDA	No suggestion	RDA		2.4 μg		2.4 μg	2.4 μg
Niacin	14–16 mg	Unknown	None	Up to the RDA[e]	Not specified	14–16 mg	Up to the RDA[e]	14–16 mg	14–16 mg
Biotin	30 μg[i]	Unknown	None	Up to AI[k,l]	Not specified	30 μg	Up to the RDA[e]	30 μg	30 μg
Pantothenic acid	5 mg	Unknown	None	Up to AI[k]	Not specified	5 mg	Up to the RDA[e]	5 mg	5 mg

[a] *Recommended dietary allowance (see text).*

[b] *Suggestions in the absence of levels I and II evidence in the case of protein-restricted diet (vitamins B1, B6, and riboflavin) and potassium-restricted diet (vitamin C).*

[c] *Recommended by the authors of this reference.*

[d] *Retinol equivalent.*

[e] *For patients ingesting less than the RDA.*

[f] *Recent data on vitamin A and survival raises questions about this recommendation [27,45,46].*

[g] *In patients under vitamin K antagonists.*

[h] *Vitamin K, 10 mg/d, if patient has low food vitamin K intake, especially if combined with prolonged antibiotic therapy.*

[i] *Insufficient data to make a recommendation.*

[j] *Dose refers to pyridoxine hydrochloride, which is the pharmacologically available source of vitamin B6 and which is about 82% free pyridoxine.*

[k] *AI refers to the AI rather than the recommended dietary allowance (RDA). AI is considered to be the average intake of a nutrient by apparently normal, healthy people (see text).*

[l] *Absent from Steiber and Kopple review [358].*

AI, Adequate intake; *EPO*, erythropoietin.

Reported by the authors of the current review.

activities [55]. Several medications may interfere with vitamin E metabolism or actions. These are summarized in Table 26.2.

Epidemiological studies indicate a reduced risk of coronary heart disease in men and women who have higher intakes of vitamin E from foods [56,57]. The mechanism for this protective effect is attributed to decreased oxidation of LDL cholesterol, a key step in the pathogenesis of the fatty streak, the first step in the development of the atheromatous plaque. On the other hand, vitamin E may promote synthesis and secretion of selectin, an adhesion molecule involved in the endothelial attachment of monocytes to endothelial cells, another step in atherogenesis [58]. However, as with vitamin A, large-scale clinical trials have failed to demonstrate a benefit of vitamin E for the prevention of cancer or CV disease [13].

Vitamin E intake in chronic kidney disease patients

In a large cohort of healthy subjects without CKD, people who were in the upper quintiles for dietary intake of folates, vitamins B12, C, and E, as well as magnesium and potassium, displayed a significantly lower incidence of CKD during follow-up. This is in opposition to the higher incidence of CKD in people who are in the higher quintile for sodium intake [14]. Different amounts of vitamins A, B2, B3, B6, and phosphate, calcium, selenium, and zinc had no association with the incidence of CKD. Vitamin E intake is slightly decreased in CKD patients ingesting protein-restricted diets (Table 26.3). In 210 nondialyzed CKD patients, Chan et al. [16] identified an insufficient vitamin E intake in 61.8% of the patients. Jankowska et al. [4] found vitamin E intake to be below the EAR in 58%–75% of CKD, MHD, CPD, and kidney transplant patients. Bossola et al. [3] confirmed from 3-day diet diaries in 128 MHD Italian patients that 66.7% of the patients had vitamin E intakes below the RDI.

Vitamin E nutritional status in chronic kidney disease 1–5D, kidney transplant, and acute kidney injury patients

In nondialyzed patients with advanced CKD, plasma vitamin E levels are usually within the normal range [59]. Malnutrition may influence vitamin E status; lower serum α-tocopherol levels are found in malnourished CKD patients compared to well-nourished individuals [60]. Peuchant et al. [61] found decreased α-tocopherol in red blood cells (RBCs) from nondialyzed CKD patients who had increased erythrocyte peroxidation, as indicated by elevated intraerythrocyte malondialdehyde (MDA) concentrations. In MHD patients, no difference in plasma vitamin E concentrations are found between pre- and postdialysis samples [31]. Serum α-tocopherol levels in MHD patients are reported to be low [31], normal [59], or increased [15,27]. Bataille et al. [27] found, in nonselected MHD patients, high levels of serum tocopherol in 72.4% of the patients, whereas only 2.4% had low levels. In CPD patients, data regarding vitamin E status are also conflictory. In 40 kidney transplant patients, McGrath et al. [62] found vitamin E to be normal both in 20 patients who were receiving cyclosporine and in 20 patients receiving azathioprine (AZA) and glucocorticoids. In critically ill patients with AKI, plasma vitamin E levels are decreased whether or not they are treated with continuous hemofiltration [63]. Vitamin E was not detectable in the spent dialysate in AKI patients treated with CVVHD.

Vitamin E, oxidant stress, and contrast-induced nephropathy in chronic kidney disease

Much evidence indicates that nondialyzed advanced CKD patients and MHD and CPD patients suffer from oxidant stress, and this condition is associated with adverse CV complications [64] [see Chapter 8: Catalytic (Labile) Iron in Kidney Disease]. Many studies have examined the effects of oral vitamin E supplementation on oxidant stress, and this has been extensively analyzed by Coombes and Fassett [65]. Most studies using α-tocopherol showed that it reduces markers of oxidant stress. The SPACE study was a randomized controlled trial of 196 MHD patients that found oral vitamin E, 800 IU/d, was of beneficial effect in the secondary prevention of CV events [66]. However, the HOPE study did not show clinical benefits of vitamin E supplements in individuals with or without chronic renal insufficiency [67,68]. Moreover, subsequent analysis of the HOPE trial and its extension (HOPE-TOO) indicated an increased risk of heart failure in patients receiving long-term vitamin E supplements [69]. Other trials involving small numbers of MHD and/or CAPD patients have shown that α-tocopherol therapy has a number of potentially beneficial effects, including vitamin E enrichment of LDL [70], improved endothelial function in diabetic MHD patients [71], increased erythrocyte life span or reduced doses of erythropoietin-stimulating agents (ESA) [72,73], and decreased LDL susceptibility to oxidation [74]. In renal transplant patients, oxidative damage is particularly likely to occur at several steps during the actual transplantation process. Reperfusion after cold ischemia may lead to marked oxidative bursts in the kidney. An antioxidant mixture that included 10 mg of α-tocopherol, given 30 minutes before reperfusion, was able to reduce the degree of lipid peroxidation as assessed by the plasma MDA levels [75]. Cristol et al. [76] found evidence for increased oxidative stress in 77 long-standing kidney transplant recipients, including individuals with and without chronic rejection. Oxidative stress appeared to be greater in the patients with chronic rejection. Patients treated with tacrolimus were found to have increased susceptibility to oxidation when compared to cyclosporine-treated patients [77]. However, McGrath et al. [62] did not observe differences in plasma TBARS (thiobarbituric acid reactive substances) and plasma vitamin E concentrations in patients receiving cyclosporine or AZA when compared to controls. There does not appear to be enough evidence yet to recommend the routine administration of α-tocopherol to renal transplant recipients [78].

Recently, vitamin E has been evaluated with regard to preventing contrast-induced nephropathy (CIN). Rezaei et al. [79] conducted a double-blind, placebo-controlled trial in 300 patients with estimated GFR (eGFR) < 60 mL/min/1.73 m^2 and undergoing coronary angiography. Patients were randomized to receive a saline infusion or a saline infusion plus 1000 mg of vitamin E. The incidence of CIN was significantly reduced in the vitamin E group (6.7% vs 14.1%) with an odds ratio by multivariate analysis of 0.41 [79]. In a metaanalysis, including 19 trials, the relative risk of CIN was reduced to 0.39 (95% CI 0.24−0.62, $P < .0001$) by adding vitamin E versus saline [80].

Vitamin E−coated hemodialysis membranes

Whether vitamin E−coated membranes will reduce oxidative stress during HD treatment has been investigated. Most clinical trials with these membranes were carried out for at least 3 months; the membranes appear to increase plasma or RBC vitamin E levels [81] and decrease plasma MDA [82]. Other observed potentially beneficial effects of vitamin E−coated membranes include decreased neutrophil activation, reduced prooxidant leukocyte activity, decreased intradialytic IL-6 production, lower serum oxidized-LDL and ADMA (asymmetrical dimethylarginine), and reduced oxidative damage to DNA. In a 6-month controlled trial, the use of vitamin E−coated dialyzer membranes decreased serum CRP and oxidized-LDL levels [83]. Regarding the response to ESA, the results are conflicting. Comparing MHD patients treated with vitamin E−coated polysulfone membrane versus those treated with standard polysulfone for 1 year, Sanaka et al. [84] found no effect of vitamin E, whereas a more recent trial [85] described a decrease in the erythropoietin (EPO) resistance index with vitamin E. No trial has yet examined the effect of these vitamin E−coated membranes on morbidity or mortality.

Vitamin E and cramps in maintenance hemodialysis patients

Vitamin E alone, or combined with vitamin C, is reported to reduce the incidence of muscle cramps in MHD patients [86].

Vitamin E supplementation in chronic kidney disease, chronic dialysis, and kidney transplant patients

The SPACE study [66] and the well-recognized prooxidant state of uremia would support the use of α-tocopherol supplements in chronic dialysis patients to prevent CV events. However, the HOPE study did not show clinical benefits of supplemental vitamin E, 400 IU/d, supplements in individuals with or without chronic renal insufficiency [67,68]. Moreover, subsequent analyses of the HOPE trial and its extension (HOPE-TOO) have shown an increased risk of heart failure in patients receiving this vitamin E supplement [69]. People without kidney disease who were given pharmacological doses of vitamin E have displayed platelet dysfunction and interference with the vitamin K−dependent coagulation factors [87]. Miller et al. [88], in a meta-analysis, including 19 trials with 135,967 patients, not specifically with CKD, found increased mortality with high doses of vitamin E therapy (≥400 IU/d). Since the benefits of vitamin E reported in the SPACE trial have not been confirmed and because of the risks of increased morbidity and mortality with high vitamin E doses, it would appear prudent to wait for more data before recommending supplemental daily vitamin E for CKD 3−5D and transplant patients. This recommendation is consistent with the KDOQI nutrition in CKD update [1] (Table 26.4).

Summary:

- Reports on the vitamin E status of CKD patients are conflicting.
- A majority of nondialyzed, advanced CKD, MHD, and CPD patients have low vitamin E intakes.
- Critically ill patients with AKI often have low serum levels of vitamin E.
- The SPACE study, which showed a lower incidence of CV events in MHD patients receiving vitamin E therapy, has not been confirmed.
- The HOPE-TOO analysis has raised questions concerning the long-term safety of vitamin E supplements.
- There are no studies concerning the effects of vitamin E−coated hemodialysis membranes on morbidity or mortality in MHD patients.
- Vitamin E appears to be effective for preventing CIN.
- No routine supplementation of vitamin E is indicated in CKD, dialysis, and transplant patients because of the paucity of clinical benefits reported and potential vitamin E toxicity.

Vitamin K, physiology, biochemistry, and nutritional status in chronic kidney disease patients

Vitamin K physiology and biochemistry

Vitamin K metabolism has been extensively reviewed [89–92]. Two classes of compounds, phylloquinone (K1) and menaquinones (K2), are primarily responsible for vitamin K activity. Phylloquinone (Table 26.1) is primarily found in green and leafy vegetables (e.g., spinach, kale, cabbage, and broccoli). Menaquinones are of bacterial origin and are found in fermented food, meat, and dairy products and represent 25% of the total vitamin K intake. The intestinal absorption of these compounds requires biliary and pancreatic juices and occurs in the small bowel where vitamin K is incorporated into chylomicrons. The importance of intestinal bacterial synthesis of vitamin K (menaquinone) as a vitamin source is still controversial. Its importance had been emphasized because of the frequency of vitamin K deficiency associated with the use of large-spectrum antibiotics. However, antibiotic therapy is not necessary for the development of vitamin K deficiency. Moreover, certain antibiotics may promote vitamin K deficiency by an independent mechanism. Antibiotics that have an *N*-methyl-5-thiotetrazole side chain, like cefamandole and cefoperazone, have a warfarin-like effect and interfere directly with the gamma-carboxylation of proteins, independently of any suppression of intestinal flora [87]. Furthermore, a vitamin K1 deficient state is easily induced experimentally by restricting food for a few days or weeks. This leads to decreased levels of plasma descarboxy-prothrombin (currently referred to as PIVKA-2, see later) and reduced urinary excretion of gamma-carboxyglutamic acid [93]. Finally and more specifically, the effect of phosphate binders on vitamin K intestinal absorption have been recently reviewed [94]. Menaquinone absorption is impaired by calcium-based and lanthanum binders. Sevelamer hydrochloride and sevelamer carbonate impair absorption of liposoluble vitamins, including vitamin K. No data are currently available regarding the vitamin K effects of iron-based phosphate binders. Other medications, beside sevelamer and vitamin K antagonists (VKAs), may interfere with vitamin K metabolism. They are summarized in Table 26.2.

The uptake of vitamin K by the liver depends on β-lipoproteins and the clearance of the plasma chylomicron remnants, including its apo-E component. There is no specific carrier for vitamin K in plasma. Plasma phylloquinone levels are found to be lower in elderly individuals as compared to young subjects [95]. Vitamin K turnover is rapid, and the body pool is small (Table 26.1). The kidney has no major role in vitamin K metabolism [91].

Vitamin K is a coenzyme for the posttranslational carboxylation of glutamate residues in several proteins, which results in gamma-carboxyglutamate (Gla) residues on these latter proteins. These latter proteins are called Gla-proteins, and they may be highly functional (see next). The Gla-residue in protein binds to calcium. In the process of forming the Gla-residue, vitamin K is transformed from the hydroquinone form (KH2) to the epoxide form (KO), releasing during this process the amount of energy required to generate the carboxylation reaction. The epoxide form of vitamin K is then recycled back to the hydroquinone form; thus a rather small quantity of vitamin K can generate a much larger amount of the Gla proteins. Indeed, the urinary excretion of Gla residues is 200–500 times greater than the dietary intake of vitamin K. The currently known Gla-proteins are found in the coagulation cascade, in bone and dentin, in microsomes of tubular cells [96], and in atherogenic plaques. The importance of vitamin K for the normal coagulation cascade is well known. In fact, the name "vitamin K" reflects this association (K for koagulation). The procoagulant factors that contain Gla residues, and hence require vitamin K for their posttranslational carboxylation, are prothrombin (Factor II), proconvertin (Factor VII), Christmas factor (Factor IX), and Stuart factor (Factor X). The anticoagulation effect of coumarin derivatives is related to the blockade of the dithiol-dependent reductases that are necessary for the recycling of vitamin K. However, the production of several inhibitors of coagulation is also vitamin K dependent, including proteins C, S, and Z. This is the explanation for the uncommon and paradoxical thrombotic complications of coumarin therapy, such as skin necrosis [97].

Two Gla-proteins, osteocalcin and matrix Gla protein (MGP), are also present in bone. Osteocalcin is the most abundant noncollagenous protein of bone and is a specific marker for osteoblast activity. In vitro, osteocalcin binds to hydroxyapatite and inhibits its formation. This action requires the vitamin K–dependent carboxylation of the protein. MGP regulates calcium deposition in the tissues. MGP knockout mice present with extensive lethal vascular calcifications [98]. The carboxylated proteins in bone play a key role in bone homeostasis. Women with hip fractures have been found to have lower plasma vitamin K levels [99], and the Hordaland Health Study has shown that hip fracture is associated with a low vitamin K1 intake [100]. It has been suggested that patients receiving warfarin therapy have greater bone density loss, but this remains controversial [101,102]. Whereas the phylloquinone (vitamin K1) is mainly retained in the liver where it carboxylates the proteins of the coagulation cascade, menaquinone derivatives (vitamin K2) have longer half-lives and are distributed in extrahepatic tissues, such as bone and vessels [91].

Assessment of vitamin K status is complex and has been recently reviewed [103,104]. For direct assessment of plasma vitamin K, the reference method is HPLC. Accuracy of this method is complicated by important interference from lipids and the need for improved electrochemical detection to enhance sensitivity and specificity. Combined HPLC and mass spectrometry (tandem technique) have provided high sensitivity and specificity results, especially for menaquinone, the assessment of which is hampered by triglyceride interference when classical methods are used. Several functional markers are more effective for detecting vitamin K functional deficiency. Prothrombin time is not a reliable test to assess vitamin K status. PIVKA-2 (des-gamma-carboxy prothrombin induced by vitamin K absence-Factor II) reflects hepatic vitamin K functionality. It decreases with vitamin K supplementation and increases with VKAs. Dephosphorylated-uncarboxylated MGP (dp-ucMGP), dephosphorylated-carboxylated MGP (dp-cMGP), uncarboxylated osteocalcin, and Gas-6 (inhibitor of vascular smooth cells calcifications) reflect extrahepatic vitamin K functionality. Regarding osteocalcin, its specificity for vitamin K function is disputed, especially in dialysis patients, because plasma osteocalcin levels are influenced by vitamin D and parathyroid hormone (PTH), which are both frequently altered in CKD. dp-ucMGP is a good indicator of vitamin K functionality, but it is not easy to measure dp-ucMGP in a typical clinical laboratory.

Vitamin K intake in chronic kidney disease patients

Data regarding vitamin K intake in nondialyzed advanced CKD patients and chronic dialysis patients are scarce. In several studies concerning intake of various vitamins in these patients, their vitamin K intake was not addressed (see later). Protein-restricted diets are most likely to contain low quantities of several vitamins, including vitamin K (Table 26.3). Cranenburg et al. [105] reported on 4-day food records from 40 MHD patients who had low intakes of vitamins K1 and K2. The intake was lower on dialysis days and during the weekend. Prescribed diets for MHD patients, which commonly are restricted in leafy vegetables to prevent potassium load and in cheese to restrict phosphate intake, were proposed as an explanation for the low vitamin K intake. Low vitamin K intake in chronic dialysis patients has been confirmed by Fusaro et al. [106] who compared the vitamin K1 intake from 7-day food questionnaires in 91 MHD patients. They found that 71.5%−89.2% of the patients had a vitamin K1 intake below the Italian recommendations.

Vitamin K nutritional status in nondialyzed chronic kidney disease, chronic dialysis, and kidney transplant patients

There has been growing interest regarding vitamin K in both CKD and chronic dialysis patients because vascular calcification in CKD patients is highly prevalent and because the use of medicines that are VKAs is strongly associated with calciphylaxis, a life-threatening condition that occurs mainly in MHD patients. In the past, few studies systematically examined the vitamin K status of CKD and chronic dialysis patients, and the results were conflicting. Plasma vitamin K levels were found to be normal by Malyszko et al. [107] in advanced CKD, MHD, CPD, and kidney transplant patients. Robert et al. [108] reported a high plasma level of phylloquinone in MHD patients. In contrast, low plasma phylloquinone levels were described in some advanced CKD (6%), MHD (29%), and CPD (24%) patients [109−111]. However, the plasma phylloquinone level itself is not a sensitive indicator of subclinical vitamin K deficiency. In 172 nondialyzed CKD 3−5D patients [112], the plasma phylloquinone level was found to be normal in 94% of the patients; but 60% of the patients had serum uncarboxylated osteocalcin >20% (a deficiency threshold), which is a marker of vitamin K deficiency associated with both advanced CKD and high serum CRP levels. Also 97% of the patients had subclinically deficient liver vitamin K levels as assessed from the serum level of PIVKA-2. This latter marker was significantly associated with serum triglycerides and the apo-E4 allele and was inversely correlated with vitamin K intake. In another cohort of 107 CKD 3−5 and dialysis patients, serum dp-ucMGP increased with the stage of CKD and was positively and independently related to vascular calcifications and patient survival [110,113]. In 50 MHD patients, Aoun et al. [114] found that 98% had vitamin K deficiency based on plasma dp-ucMGP. In 188 MHD patients compared to 88 healthy controls, Schlieper et al. [115] confirmed that vitamin K deficiency was common in chronic dialysis patients. They found increased PIVKA-II in 64% of the patients; plasma dp-cMGP and dp-ucMGP levels were, respectively, 3.3- and 6.5-fold greater than in controls. In 28 CPD patients, Stankowiak-Kulpa et al. [116] reported increased plasma PIVKA-II levels indicating vitamin K deficiency, whereas prothrombin time and INR were normal. In 518 kidney transplant patients [117], serum dp-ucMGP was reported to be above the normal range in 91% of the patients indicating vitamin K deficiency. However, Jansz et al. [118] reported lower serum uc-dpMGP levels reflecting better vitamin K status in kidney transplant recipients compared to chronic dialysis patients. In addition to an improvement in GFR and food intake in renal transplant patients, the withdrawal of sevelamer therapy was considered to be an important factor associated with improvement in vitamin K status, because serum uc-dpMGP decreased significantly after sevelamer monotherapy was discontinued. Thus phosphate binders may predispose to vitamin K deficiency in chronic dialysis patients, as previously mentioned.

Clinical effects of vitamin K deficiency in chronic kidney disease

Glomerular filtration rate decline

In people without CKD, Wei et al. [119] reported that high serum levels of dp-ucMGP were a risk factor for GFR decline.

Bone status in chronic kidney disease patients

The effect of vitamin K supplementation on bone health in the general population is controversial [120]. Apalset et al. [100] in the Hordaland study in Norway (the male and female subjects were between 71 and 75 years of age) reported that people in the lower quartile of vitamin K1 intake were at a 57% increased risk of hip fracture, whereas the quartile of vitamin K2 intake or the presence of the apo-E4 genotype was not associated with increased risk. Caluwe et al. [103] reviewed 17 trials regarding the effects of vitamin K supplements on bone mineral density in non-CKD patients. The results were contradictory. The authors commented that some of the trials were lacking power, and that low compliance might have diminished the benefits of vitamin K supplementation.

Two decades ago, in MHD patients an inverse relationship was reported between a history of bone fractures and the plasma phylloquinone levels or the proportion of carboxylated versus noncarboxylated osteocalcin in plasma [121]. Serum PTH levels were high (>300 ng/L) only in patients with low plasma phylloquinone concentrations. These latter patients also had an abnormally high incidence of the apo-E3/4 and E4/4 genotype which may indicate impaired tissue uptake of phylloquinone from chylomicrons [122]. MHD patients with adynamic bone disease who received vitamin K supplements for 1 year displayed both a significant increase in serum PTH, alkaline phosphatase, and the cross-linked N-terminal telopeptide of type I collagen and a trend toward decreased serum osteoprotegerin, a well-recognized factor associated with vascular calcification [123]. More recently, Fusaro et al. [124] compared the prevalence of vertebral fractures and osteocalcin in MHD patients with or without prescription of VKAs. Male patients prescribed VKAs had a significantly higher frequency of vertebral fractures and lower plasma osteocalcin levels.

Vascular calcifications, calciphylaxis, and outcomes

Aoun et al. [114] reported a linear relationship between the plasma dp-ucMGP and the aortic calcification (AC-24) score (Fig. 26.3). The frequently altered

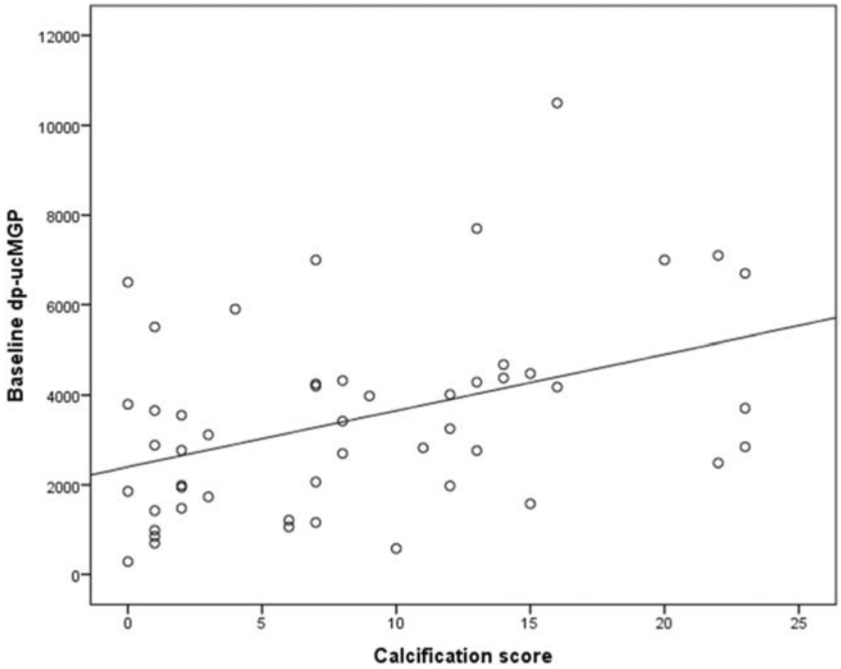

FIGURE 26.3 Relationship between plasma dp-ucMGP concentrations and aortic calcification severity score ($r = 0.43$; $P = .002$). *dp-ucMGP*, Dephosphorylated-uncarboxylated matrix Gla protein. *Source: Reproduced from Aoun M, Makki M, Azar H, Matta H, Chelala DN. High dephosphorylated-uncarboxylated MGP in hemodialysis patients: risk factors and response to vitamin K2, a pre-post intervention clinical trial. BMC Nephrol 2017;18:191. Reproduced with permission from the Editor.*

status of vitamin K in advanced CKD patients and its association with vascular calcification and outcomes were recently reviewed [103]. Most, but not all, of the studies reported a positive relationship between ucMGP and vascular calcification and/or overall mortality in CKD, in chronic dialysis, and kidney transplant patients [103]. In 350 CKD patients (nondialyzed and chronic dialysis patients), plasma dp-ucMGP was positively associated with a high vascular calcification score and/or vascular stiffness. Also, all-cause mortality was associated with increased plasma dp-ucMGP in 706 MHD and kidney transplant patients. Delanaye et al. [125] found in 160 MHD patients a significant, positive relationship between plasma dp-ucMGP and the calcification score (Kauppila method). It is noteworthy that the plasma dp-ucMGP levels were dependent on whether patients were receiving VKA therapy. Also, in 518 kidney transplant recipients [117], plasma dp-ucMGP was above the normal range in 91% of the patients, indicating vitamin K deficiency. During an average follow-up of 9.8 years, patients in the highest quartile of plasma dp-ucMGP concentrations had a significantly higher risk of mortality (HR: 3.10; 95% CI, 1.87–5.12; $P < .001$). Moreover, an altered ratio in plasma of carboxylated:uncarboxylated MGP was strongly associated with calciphylaxis in 20 MHD patients as compared to 20 matched patients who did not have this altered ratio [126]. VKAs are a recognized risk factor for calciphylaxis [127]. The association of prescribed VKA and increased ucMGP with arterial calcifications has been reported in young subjects without CKD [128]. In 387 MHD patients, warfarin was significantly associated with aortic and iliac calcifications in a multivariate analysis (odds ratio >2 for both the aorta and the iliac) [129]. Notwithstanding the increased risk of plasma uc/cMGP imbalances with VKA treatment, other analyses of potential benefits versus risks associated with VKA treatment have given conflicting results [130,131].

Vitamin K supplementation in chronic kidney disease, chronic dialysis, and kidney transplant patients

Because of the high risk of thrombosis associated with the nephrotic syndrome and the frequent need for coumarin derivatives for its prevention, vitamin K supplements are not routinely recommended for nephrotic patients. Since CKD 3–5D patients are usually not considered to have vitamin K deficiency, as determined by the more commonly performed measures of altered clotting factors or clotting function, vitamin K supplements generally have not been recommended (Table 26.4). Traditionally, vitamin K supplements have been proposed for patients who are eating poorly and receiving antibiotics that may suppress intestinal bacteria that synthesize vitamin K; these patients tend to be considered at increased risk for developing vitamin K deficiency, particularly when these latter conditions persist for extended periods of time. Patients receiving TPN as their sole nutritional source for more than 1 or 2 weeks should also receive supplemental vitamin K. On the other hand, it has been suggested that vitamin K status should be assessed using serum dp-ucMGP to determine whether CKD 3–5D patients should receive vitamin K supplements. At present, the evidence supporting vitamin K supplements to correct high levels of serum dp-ucMGP or to reduce the risk of arterial calcification is not considered to be conclusive. On the other hand, in MHD patients, Westenfeld et al. [132] were able to reduce serum dp-ucMGP with vitamin K2 supplements in a dose-dependent fashion. After the supplements were terminated, during the washout period, serum dp-ucMGP increased again. Vitamin K2, which facilitates the carboxylation of MGP, may be a suitable therapeutic agent to decrease vascular calcification. Several clinical trials are currently underway to evaluate the effect of vitamin K supplements on vascular calcification and CV outcomes (e.g., iPACK-HD, NCT01528800; VitK-CUA NCT02278692; Vita VasK, NCT01742273). Because of the risks of treating patients with vitamin K, many physicians are now using the NOAC (new oral anticoagulants) instead of vitamin K. Care must be taken, because many of these nonvitamin K anticoagulants are primarily excreted by the kidney and might become toxic in advanced kidney failure.

Summary:

- Vitamin K acts at the hepatic, vascular, and bone level where it catalyzes the carboxylation of specific proteins that help to prevent excessive clotting and calcification of soft tissues, including blood vessels, and that promote normal bone metabolism.
- Data on the amount of vitamin K intake in CKD patients are lacking.
- Subclinical vitamin K deficiency, as determined by increased plasma PIVAK-2 and ucMGP levels, is frequent in CKD patients and is worsened by VKAs.
- Measurements in clinical laboratories of plasma PIVAK-2 and ucMGP are not yet routinely available.
- Vitamin K deficiency and the lack of clinically available testing for PIVAK-2 and ucMGP increase the risk of arterial calcification and of calciphylaxis.

Continued

- The effects of vitamin K supplements on vascular calcification are currently being investigated in several clinical trials.
- At this time the routine supplementation of vitamin K is not indicated for CKD, dialysis, and kidney transplant patients; recommendations may change pending the results of clinical trials.

Vitamin B1 (thiamine), physiology, biochemistry, and nutritional status in chronic kidney disease patients

Vitamin B1 (thiamine) physiology and biochemistry

It is stated that the syndrome of beriberi has been recognized for over 4000 years [133]. In 1911 an antiberiberi principle was discovered in rice bran extracts, and in 1934 the structure of thiamine was identified. Vitamin B1 or thiamine (Table 26.1) is a compound formed by the condensation of pyrimidine and thiazole rings. Thiamine forms esters with phosphate, functionally the most important of which are thiamine pyrophosphate (TPP), monophosphate, and triphosphate (TTP). Thiamine is rather labile and may be destroyed by heat, high pH (above 8), oxidants, and ultraviolet irradiation. Thiamine is abundant in only a few foods of animal and vegetable origin. These foods include lean pork, yeast, and legumes. Because thiamine is water soluble, foods cooked with water can be leached of significant amounts of thiamine. Thiamine is absorbed from the small intestine by active and passive processes. In plasma, thiamine is mainly bound to albumin. Most thiamine in the body is present as TPP. The availability or activity of thiamine is inhibited by, among other factors, alcoholic drinks, thiaminases, folate deficiency, and protein–energy malnutrition. Catabolism of thiamine produces many metabolites that are excreted in the urine. Erythrocyte and body levels of thiamine can be indirectly assessed by measuring the erythrocyte transketolase activity (ETKA), before ($ETKA_o$) and after ($ETKA_s$) stimulation by adding TPP to the assay [134]. The ETKA stimulation index (αETKA) (i.e., the ETKA with added TPP × 100, divided by $ETKA_o$, i.e., without added TTP) is a more sensitive indicator of thiamine deficiency. TPP can be measured directly with HPLC, which has become the preferred method for measuring thiamine status in many laboratories [135]. Both whole blood thiamine and RBC TPP, the active functional form of thiamine, are measured with HPLC.

TPP plays a key role in energy metabolism [136]. It is a coenzyme for a large number of chemical reactions involving, but not limited to, carbohydrate metabolism, including oxidative decarboxylation of α-ketoacids and decarboxylation of alpha-ketoglutarate to succinyl-coenzyme A (CoA) in the citric acid cycle. This is important for the production of gamma-aminobutyric acid, an inhibitory neurotransmitter in the brain. TPP is also the coenzyme for pyruvate dehydrogenase which catalyzes the conversion of pyruvate to acetyl-CoA. Hence, thiamine deficiency may impair lactate utilization and lead to thiamine-responsive lactic acidosis [137]. As indicated earlier, thiamine is a coenzyme for the transketolase reaction which is an integral part of the pentose phosphate pathway. Transketolase is found abundantly in myelinated structures of nervous tissues [138]. This may account for the peripheral neuropathy that occurs in beriberi. Thiamine deficiency has been associated with several syndromes involving the central and peripheral nervous systems, such as peripheral neuropathy and/or the Wernicke–Korsakoff syndrome in chronic alcoholism and in dry beriberi, and in cardiomyopathy with heart failure in wet beriberi. These clinical syndromes of thiamine deficiency are not often encountered today but are still occasionally observed (see next) [139–141]. Moreover, inborn errors of thiamine transporters are now well identified, and five phenotypes associated with these genetic disorders are described: megaloblastic anemia, deafness and diabetes in SLC19A2 defects, and peripheral neuropathy and encephalopathy in SLC19A3, SLC25A19, and TPK1 genetic defects [142]. Several medications may also interfere with thiamine metabolism or actions. They are summarized in Table 26.2.

Dietary vitamin B1 intake in chronic kidney disease patients

Restriction of foods rich in potassium does not interfere with dietary thiamine intake. Thiamine intake has been reported to remain at or above the RDA when the protein intake is at least 40–80 g/d (see Table 26.2 from Stein et al. [15]). Among 210 CKD patients, thiamine intake averaged 136% of the recommended intake [16], but intake remained below the recommendation in 37% of the patients. However, Jankowska et al. [4] identified inadequate daily thiamine intake (i.e., below the EAR) in 62% of CKD patients, 58% of MHD patients, and 48% of kidney transplant recipients who were not receiving vitamin supplements. In CPD patients, 65% of the patients were below the EAR for thiamine, confirming previous reports. Wang et al. [17] reported an average daily intake of about 50% of the RDA in 242 CPD patients, both male and female. Their thiamine intake was independently related to total urea clearance and RRF, possibly because less efficient dialysis is associated with decreased protein intake. Also, Martin-Del-Campo et al. [18] found that approximately 30% of 67 CPD patients had a daily thiamine intake below the recommended intake. Eating habits influence the amount of vitamins ingested by CKD or maintenance dialysis patients, and this also appears to be the case for thiamine. Of MHD patients, 73.7% who were in the habit of eating dinner, a meal associated with a better quality of ingested food (higher protein and lower lipid contents), met the recommended intake for thiamine as compared to 45.5% patients who often did not eat dinner [143]. These data also underscore the nutritional superiority of traditional foods and cooking in comparison to most processed foods. Bossola et al. [3] reported, from 3-day diet diaries, that 92% of 128 Italian MHD patients had a vitamin B1 intake below the RDI. Data from a 7-day food questionnaire obtained from seven MHD patients indicated that the intake of vitamin C, thiamine, riboflavin, and niacin was not different between the day of dialysis and an interdialytic day, but these findings are limited by the small number of patients studied [144].

Vitamin B1 (thiamine) nutritional status in chronic kidney disease, maintenance hemodialysis, chronic peritoneal dialysis, kidney transplant, and acute kidney injury patients

The effects of CKD on thiamine metabolism remain unclear. In Sprague−Dawley rats after 5/6 nephrectomy, thiamine transporters were markedly decreased in the small intestine, heart, and liver when compared to sham-operated control rats, whereas plasma thiamine levels were not different between the two groups [145]. Thus intestinal absorption of thiamine and its availability at the organ level might be impaired in CKD. The ETKA stimulation index was found to be normal by Kopple et al. [146] in 15 nondialyzed advanced CKD patients who were receiving 1 mg/d thiamine HCl supplements. No relationship was observed between ETKA or the ETKA stimulation index and the level of GFR. In 33 adults with the nephrotic syndrome, erythrocyte TPP was normal [147]. Other investigators reported that the blood thiamine levels are usually in the normal range in MHD patients [148]. However, uremic toxins may impair thiamine function. In the early days of chronic dialysis therapy, Lonergan et al. reported a dialyzable compound in uremic serum that inhibited ETKA and suggested that it might be guanidinosuccinic acid [149]. This inhibitory effect of uremic sera was ameliorated by dialysis treatment. Sterzel et al. [150] reported that transketolase activity of nervous tissue was inhibited by uremic plasma, by cerebrospinal fluid from uremic patients and by a low molecular weight (MW) fraction (<500 kDa) of dialysate. Kopple et al. [146] did not find acute changes in ETKA observed during a single HD treatment. Kuriyama confirmed a low basal ETKA (ETKA$_o$) and stimulated ETKA (ETKA$_s$) in a group of 72 MHD, CPD, and nondialyzed CKD patients, even though they had high blood thiamine levels following the ingestion of thiamine supplements [151]. These findings are consistent with a circulating inhibitor of ETKA in chronic kidney failure.

In 43 nonsupplemented MHD patients, Descombes et al. found low or marginal ETKA$_o$ in 56% of MHD patients, and an increased ETKA stimulation index in 21% of the MHD patients [152]. In ETKA$_o$ deficient patients, whole blood thiamine was normal. The functional deficiency was reversed with large amounts of thiamine hydrochloride (100 mg after each HD). In the same study, patients undergoing MHD with a polyacrylonitrile membrane dialyzer had lower ETKA$_o$ than those treated with cellulose acetate; these findings raise the question of a possible role of high hemodialyzer membrane flux as a cause of thiamine deficiency. Heinz et al. [153] reported that the HD procedure induces a greater decrease in plasma thiamine levels with high-flux versus low-flux membranes. Saka et al. [154] analyzed the thiamine status using HPLC before the first HD session in 241 incident MHD patients not receiving vitamin supplements. Whole blood thiamine levels were below the normal range in 12.4% of the patients and were inversely correlated with age and positively correlated with Barthel index (a physical function score), diastolic blood pressure, BMI, and hemoglobin. Surprisingly, using stepwise logistic regression analysis, the Barthel index remained the only variable associated with blood thiamine levels. In 100 MHD patients, Ubukata et al. [155] did not observe low serum thiamine levels in MHD patients, and only 18% of patients exhibited a post-HD decrease in serum thiamine. The prescribed membranes were high flux, but the prescribed blood flow was low (≤250 mL/min). Jankowska et al. [156] found a significant decrease in whole blood TPP during the HD session (i.e., a decrease of 43.9% with a wide coefficient of variation, 71.5%). The TPP decrease was inversely correlated with the patient's body weight but not with the membrane flux. This is surprising because thiamine is bound to albumin in plasma. Despite the decrease in TPP during the HD session, only one patient had a blood TPP below normal. Thiamine intake and supplements were not found to be correlated with the whole blood TPP levels, casting doubts about altered intestinal absorption of thiamine in CKD patients as was suggested in the experiment on CKD rats mentioned earlier [145]. Coveney et al. [157] reported lower blood thiamine in patients treated with extended dialysis sessions when compared to patients treated by conventional dialysis. However, as reported in several previous studies, no patient had abnormally low blood thiamine. Hence, thiamine losses during the HD procedure and nutritional status of thiamine in chronic dialysis patients remain controversial.

Blumberg et al. [158], and Boeschoten and coworkers [32] reported thiamine deficiency in 50% and 26%, respectively, of CPD patients who were not receiving thiamine supplements. Losses of this vitamin into the peritoneal dialysate were identified but were substantially lower than the normal daily urine excretion of thiamine [32]. Jankowska et al. [159] also identified TTP in peritoneal effluent from 26 patients treated either with CAPD or automated peritoneal dialysis. The losses were low in most patients, independent of thiamine supplementation, but in two patients they were close to the RDA for thiamine. Analyzing the TPP losses during the peritoneal equilibrium test, the authors concluded that clearance of TPP was, to some extent, typical for smaller molecules. However, the amount of TPP in the 24-hour effluent was higher than in the plasma, independent of glucose transfer and convective transport, raising the possibility of active TPP transport by the peritoneal membrane or local synthesis. This is an important question which should be addressed in further research. Recently, in 75 AKI patients, serum vitamin B1 (thiamine) was found deficient only in 16% of the patients, much less than for vitamin B6 (67%), vitamin C (87%), and folate (33%) [160].

The question of functional vitamin B1 deficiency in the presence of normal thiamine levels was addressed in a recent study by Zhang et al. [161]. The authors measured both plasma and RBC thiamine and TPP levels using HPLC and ETKA in 16 CPD patients, 16 MHD patients, and 16 controls. They also assessed oxythiamine and oxythiamine pyrophosphate (OTPP), an inhibitor of TPP-dependent enzymes that accumulates in kidney failure. Plasma and RBC thiamine levels were increased in both CPD and MHD patients, whereas the RBC transketolase activity ($ETKA_o$) was decreased in MHD patients by 41% compared to controls. Adding TPP in excess (i.e., an $ETKA_s$) had no effect on ETKA in controls, but ETKA increased significantly in MHD patients, supporting the hypothesis of displacement of a competitive inhibitor by TPP. Plasma oxythiamine levels were increased 4-fold in the CPD patients and 15-fold in the MHD patients as compared to healthy controls. Oxythiamine decreased by 53% after a dialysis session. These data suggest that oxythiamine accounted for most of the ETKA inhibition, as reflected in the relationship between RBC OTPP and ETKA inhibition. However, in vitro RBC studies indicated that the inhibition was reversible; a high concentration of thiamine was able to reverse the reduced ETKA. These data support the thesis that there may be a discordance between normal plasma concentrations and impaired functional activity of a vitamin due to the accumulation of molecules that competitively inhibit the actions of the vitamin.

Clinical significance of thiamine deficiency in chronic kidney disease patients

Clinical manifestations of thiamine deficiency have rarely been described in end-stage kidney disease (ESKD) patients. Beriberi was reported in two MHD patients decades ago [162,163]. Several cases of lactic acidosis, hyperglycemia, and compromised hemodynamics reversed by thiamine injections occurring early after kidney transplantation have been reported in adults [164,165] and in a child [140]. Case reports of Wernicke's encephalopathy are increasing in frequency. They are described in MHD and CPD patients but may often be overlooked because the classical triad of this syndrome (confusional state, ataxia, and ophthalmoplegia) is present in only 20% of cases [166–169]. In the report by Ueda et al. [169], typical pathologic lesions of Wernicke's encephalopathy were found in five patients who had been given such other diagnoses by clinicians as uremic encephalopathy, disequilibrium syndrome, dialysis dementia, or brainstem hemorrhage. Also, chorea has been reported in two cases of thiamine deficiency in MHD patients [170]. The same authors found thiamine deficiency in 10 MHD patients presenting with mental disturbances; 9 out of 10 recovered with intravenous thiamine supplementation [171]. Infection, surgery, and large glucose loads may increase the nutritional needs for thiamine, and precipitate clinical manifestations of thiamine deficiency.

Recently, treatment with large doses of thiamine and ascorbic acid in association with glucocorticoids (ATS) has been proposed to improve the outcomes in critically ill patients with such conditions as pneumonia [172] or septic shock [173,174]. See also the vitamin C (ascorbic acid) discussion later. The rationale for treatment with thiamine and vitamin C prescriptions is that these vitamins are frequently depleted in these conditions, and thiamine is critical for normal lactate metabolism, and vitamin C has important antioxidant and antiinflammatory properties and actions on neurotransmitter synthesis. The amounts of thiamine and vitamin C given to these patients were, respectively, 400 mg/d and 6 g/d for 4 days. Three retrospective "before/after" cohorts were studied using propensity scores. In the three studies, mortality was significantly reduced in the patients receiving ATS. The incidence of AKI did not differ between the treatment and control groups in the study by Sadaka et al. [174], and the need for renal replacement therapy was significantly decreased [173] or identical for ATS versus the control groups [172]. On the other hand, Litwak et al. [175] did not confirm a survival advantage with ATS in critically patients.

Thiamine supplementation in chronic kidney disease, chronic dialysis, and kidney transplant patients

There is no specific guideline for thiamine supplementation in CKD 3–5D and CKD T1–5 patients in the recent KDOQI nutrition guidelines update except that the dietary vitamin intake of adults with CKD 1–5D and CKD T1–5 should be periodically assessed and multivitamin supplementation should be considered for individuals with inadequate vitamin intake. Also, CKD 5D patients who have inadequate dietary intake of vitamins for extended periods of time should be considered for multivitamin supplements [1]. Some investigators have recommended amounts of thiamine supplements for MHD patients ranging from 1 to 40 mg daily [152,176]. The thiamine intake from food is generally about 0.6–1.5 mg/d in advanced CKD, MHD, and CPD patients. The ETKA stimulation index and serum thiamine levels are usually normal in patients with CKD 3–5D. When thiamine deficiency is present, correction is readily obtained by feeding low quantities of thiamine. The Food and Nutrition Board recommended dietary allowances (RDAs) for thiamine for nonpregnant healthy adults are 1.1 and 1.2 mg/d, for females and males, respectively, and there is no reason to believe that the daily thiamine requirement for CKD 3–5D patients is lower than this amount. Although these patients may receive adequate thiamine from their ingested foods, their food intake not uncommonly is low, particularly when other morbid conditions are present, and as indicated earlier, thiamine deficiency has been reported in some CKD 3–5 patients. As recently suggested that oxythiamine accumulates in CKD and may act as a competitive inhibitor of thiamine. We, therefore, recommend the routine administration of a thiamine supplement of 1.2 mg/d for nondialyzed CKD 3–5, MHD and CPD patients (Table 26.4).

Summary:

- Dietary vitamin B1 (thiamine) intake is often below the RDA in advanced CKD, MHD, and CPD patients.
- Discrepancies often exist in kidney failure patients between the measurement of normal serum or plasma concentrations of vitamin B1 and impaired functional tests (e.g., ETKA and the ETKA stimulation index) which are indicators of vitamin B1 inadequacy.
- Recent data suggest a competitive inhibition of ETKA by oxythiamine and possibly other compounds that accumulate in advanced CKD.

Continued

- In advanced CKD, MHD, CPD, or kidney transplant patients who develop unusual neurological symptoms, thiamine deficiency should be considered.
- Critically ill patients with AKI often have low serum levels of thiamine.
- Treatment of acutely and severely ill patients with a combination of thiamine, vitamin C, and glucocorticosteroids (ATS), which has been used to prevent or limit the severity of AKI and to decrease mortality, remains controversial.
- It is recommended that daily thiamine supplements equal to the RDA should be routinely prescribed to advanced CKD, MHD, and CPD patients.

Vitamin B2 (riboflavin), physiology, biochemistry, and nutritional status in chronic kidney disease patients

Vitamin B2 or riboflavin physiology and biochemistry

Riboflavin (vitamin B2) is an alloxazine derivative with an MW of 376.4 (Table 26.1). The main active riboflavin compounds are flavin mononucleotide (FMN, an alloxazine ring combined with ribitol and phosphate) and flavin adenine dinucleotide (FAD, the FMN molecule modified by the addition of an activated adenosine monophosphate). Riboflavin is modestly soluble in aqueous solutions, heat-stable, and photosensitive. It is present in many plant and animal products, such as milk, eggs, bread, cereals, lean meats, and broccoli [177]. An active sodium- and glucose-dependent absorption pathway for riboflavin occurs in the proximal jejunum and is important for the transport of small quantities of this vitamin. Large amounts of riboflavin are absorbed from the intestine by passive diffusion. Bile salts appear to facilitate intestinal absorption of riboflavin. After cellular uptake, riboflavin is transformed by the action of flavokinase and FAD synthetase to FMN and the more abundant FAD which act as cofactors to enzymes called flavoproteins. Riboflavin metabolites are excreted in urine. Flavoenzymes are involved in numerous oxidation–reduction reactions that are necessary for many metabolic pathways, including energy production. The erythrocyte glutathione reductase (EGR) activity without (EGR_o) and with the saturation of this enzyme with FAD has been used to assess riboflavin status [134]. The ratio of EGR with FAD × 100 divided by EGR_o indicates the EGR stimulation index (α-EGR). The α-EGR is a rather reproducible and sensitive test, a high α-EGR indicating riboflavin deficiency. Riboflavin may be measured directly by a fluorometric method and by

HPLC, which has been used to study riboflavin in CKD patients [178]. Several medications may interfere with vitamin B2 metabolism or actions. They are summarized in Table 26.3.

Dietary riboflavin (vitamin B2) intake in advanced chronic kidney disease, maintenance hemodialysis, and chronic peritoneal dialysis patients

With protein-restricted diets the daily intake of riboflavin is reported to be low with a 40 g/d protein diet and meeting the RDA with a protein intake of 60 or 80 g/d [15]. In the study by Chan et al. [16] in 210 nondialyzed CKD patients, 41% of the patients had an insufficient intake of riboflavin, a low intake that was confirmed at the same level by Jankowska et al. [4] in 50 nondialyzed CKD patients. These latter authors also found a low daily riboflavin intake in, respectively, 58%, 47%, and 15%, respectively, of MHD, CPD, and kidney transplant patients. Wang et al. [17] also found a low riboflavin intake in most CPD patients, independent of their RRF and the adequacy of their dialysis treatments. Martin-Del-Campo et al. [18] reported that 25% of 73 Mexican CPD patients had a low intake of riboflavin, and patients in the higher quartile of serum CRP levels had significantly lower intakes of riboflavin. Bossola et al. [3] examined 3-day diet diaries from 128 Italian MHD patients and reported a daily riboflavin intake below the RDI in 74% of the patients.

Riboflavin (vitamin B2) nutritional status in advanced chronic kidney disease, chronic dialysis, and kidney transplant patients

Porrini et al. [179] reported increased α-EGR (i.e., increased EGR stimulation index), indicating riboflavin deficiency, in many nondialyzed CKD patients prescribed a low-protein diet. The clinical significance of this finding remains unknown. Most studies showed normal or increased plasma riboflavin levels in MHD and CPD patients even when they are not prescribed vitamin supplements [32,152,180], notwithstanding the losses of riboflavin into peritoneal dialysate [32] and probably hemodialysate. However, Skoupy et al. found that 18.5% of CAPD patients had increased α-EGR, indicating riboflavin deficiency [181]. On the other hand, riboflavin deficiency was not identified in 12 pediatric CPD and MHD patients who were not receiving vitamin supplements [182]. In MHD patients receiving multivitamin supplements and treated with standard or daily nocturnal HD sessions, no riboflavin deficiency was found even with the extensive dialysis treatments [183]. No clinical syndromes associated with riboflavin excess or deficiency have been reported in CKD or End-Stage Renal Disease (ESRD) patients.

Riboflavin supplementation in chronic kidney disease, chronic dialysis, and kidney transplant patients

The recommended guidelines for riboflavin supplementation in CKD 3−5D and CKD T1−5 patients in the recent KDOQI nutrition guidelines for CKD are similar to those for thiamine [1] (Table 26.4): dietary vitamin intake of adults with CKD 1−5D and CKD T1−5 should be periodically assessed, and multivitamin supplementation should be considered for individuals with inadequate vitamin intake. CKD 5D patients who have inadequate dietary intake of vitamins for extended periods of time should be considered for multivitamin supplements [1]. Recommendations by other workers in the field vary from no riboflavin supplement [32,152,184] to an amount equivalent to the RDA [185,186], which is 1.1 mg/d for nonpregnant women and 1.4 mg/d for men. Low doses of riboflavin (1 mg/d) were sufficient to normalize the α-EGR in CAPD patients [22]. For the rationale put forth for thiamine, we recommend a routine daily riboflavin supplement equal to the RDA for CKD 3−5D patients.

Summary:

- Dietary riboflavin (vitamin B2) intake is frequently reported to be below the RDA in advanced nondialyzed CKD, MHD, and CPD patients.
- Data regarding blood riboflavin (vitamin B2) levels in CKD and ESRD patients are conflictory. This may be partly due to discrepancies between the direct of measurements of plasma riboflavin concentrations and functional tests (e.g., the EGR stimulation index).
- No clinical syndromes related to riboflavin deficiency have been described in advanced CKD, chronic dialysis, or renal transplant patients.
- It is recommended that daily supplements of riboflavin equal to the RDA should be routinely prescribed to advanced CKD, MHD, and CPD patients.

Vitamin B6 (pyridoxine) physiology, biochemistry, and nutritional status in chronic kidney disease patients

Vitamin B6 physiology and biochemistry

Reference is made to previous reviews of normal vitamin B6 metabolism and function [187,188]. Vitamin B6 is composed of three derivatives of the pyridine ring: pyridoxine, pyridoxal, and pyridoxamine. Some characteristics of vitamin B6 are listed in Table 26.1. Phosphorylation in the 5 position is necessary for the biological activity of vitamin B6.

Pyridoxal-5′-phosphate (PLP) and pyridoxamine-5′-phosphate are the active coenzyme forms. Pyridoxine is mainly found in plant foods, especially wheat bran, avocado, banana, lentils, walnuts, cooked soybean, and potatoes, and pyridoxal and pyridoxamine are primarily obtained from animal products; for example, tuna, raw chicken breast, and ground beef. These compounds are absorbed by a nonsaturable, passive process in the jejunum. These three vitamers are phosphorylated in the liver by pyridoxine kinase, which requires zinc and adenosine triphosphate. PLP is derived from the other vitamers by the action of FMN oxidase and is transported in plasma bound to albumin and in red cells bound to hemoglobin. The major repository of PLP is skeletal muscle, where it is bound to glycogen phosphorylase. In liver, PLP and the other phosphorylated forms of vitamin B6 are dephosphorylated by alkaline phosphatase, leading first to pyridoxal and then 4-pyridoxic acid (4-PA) by the irreversible action of a FAD-dependent aldehyde oxidase.

Functional tests have traditionally been utilized to assess for vitamin B6 deficiency. Erythrocyte glutamate oxaloacetate transaminase (EGOT) or glutamic pyruvate transaminase (EGPT) activity is measured in the basal state ($EGOT_o$, $EGPT_o$) and after stimulation by adding excess PLP. The ratio of the stimulated-to-basal activity is the activation coefficient or index (α-EGOT and α-EGPT). If stores of the coenzyme (PLP) are adequate, the addition of an excess of the coenzyme will have only a small effect on the apoenzyme activity, and the ratio will be close to 1.0. If there is deficiency of PLP, the apoenzyme will be stimulated by the addition of the coenzyme, and the index value will be substantially greater than 1.0 [189]. Currently, plasma levels of PLP and other B6 compounds are usually measured by HPLC [189]. Several factors are associated with higher or lower plasma PLP levels. People over 65 years have lower plasma PLP levels than younger individuals. Women have lower levels than men. One explanation for these findings could be differences in muscle mass. Plasma PLP levels are inversely correlated with dietary protein intake. Tobacco smoking decreases plasma B6 levels. Increased serum acute phase proteins and alkaline phosphatase activity and impaired renal function are associated with lower plasma B6 levels [190]. Also, many medicines interfere with the actions or metabolism of vitamin B6. Many of these medicines are taken by patients with CKD (Table 26.2). The intake of these medicines must be considered when evaluating studies of the dietary requirements for vitamin B6 or when prescribing vitamin B6 intake.

PLP is a coenzyme for more than 140 enzymatic reactions [191] and particularly for those enzymes involved with the metabolism of amino acids and some lipids. PLP forms a Schiff base with the ε-amino group of lysine in many enzymes. The Schiff base alters the charge on the rest of the PLP molecule and strongly increases its reactivity, particularly to other amino acids. Vitamin B6 is essential for gluconeogenesis by facilitating, among other mechanisms, transamination and glycogen phosphorylation, for niacin formation via the PLP-dependent kynureninase which transforms tryptophan to niacin, and for normal erythrocyte metabolism by acting as coenzyme for transaminase and influencing the hemoglobin affinity for oxygen. Vitamin B6 facilitates the synthesis of several neurotransmitters and modulates the actions of certain hormones through the binding of PLP to steroid receptors.

Dietary vitamin B6 intake in chronic kidney disease patients

A high vitamin B6 intake does not appear to be associated with a lower CKD incidence in a large cohort of healthy subjects without CKD, in contrast to high intakes of folates and vitamins B12, C, and E [14]. Protein-restricted diets are not associated with low vitamin B6 intake (Table 26.3; [15]). In a recent study addressing the dietary micronutrient intakes in CKD, MHD, CPD, and renal transplant patients not receiving vitamin supplements, vitamin B6 intake was below the DRI in about 40%, 40%, 20%, and 30%, respectively, of these patients [4]. Vitamin B6 intake is often low in dietary surveys of CPD and MHD patients [158,176]. In CPD patients, Wang et al. [17] also reported inadequate intakes for B6 independently of RRF and dialysis adequacy. Martin-Del-Campo et al. [18] reported that 50% of 73 CPD patients have low intakes of vitamin B6. Dietary habits may influence the amount of vitamins ingested by CKD or maintenance dialysis patients. For example, lower intakes of vitamin B6 were found when MHD patients ingested meals of processed foods rather than home-prepared food [143].

Nutritional status of vitamin B6 in advanced chronic kidney disease, chronic dialysis, kidney transplant, and acute kidney injury patients

Blunted weight gain was observed during a 4-week period in chronically azotemic compared to sham-operated rats and was significantly more pronounced in rats that were fed a vitamin B6-deficient diet as compared to a vitamin B6−surfeit diet [192]. Mydlik et al. found plasma PLP to be significantly decreased in adult patients with the nephrotic syndrome [147]. Podda et al. [193] reported significantly decreased blood PLP concentrations in 84 nephrotic patients as compared to controls, and there was a positive correlation between the blood vitamin B6 levels and serum albumin. A high incidence of vitamin B6 deficiency in both adult and pediatric advanced CKD, MHD, and CPD patients has been observed in most, but not all studies. The use of red cell transaminase activity ($EGOT_o$ or $EGPT_o$), rather than the activation coefficient or stimulation index (α-EGOT and α-EGPT), as the criterion for deficiency has been criticized because of the shortened life span of RBCs in CKD patients and the higher activities of some enzymes in younger erythrocytes [194]. Low plasma vitamin B6 levels have also been described in AKI patients especially in individuals with AKI-2 and AKI-3 who have high illness scores and are receiving renal replacement therapy (see Chapter 35: Metabolic Management and Nutritional Support in Acute Kidney Injury).

Studies that assessed vitamin B6 status by measuring plasma PLP concentrations also found decreased levels in most dialyzed and nondialyzed advanced CKD patients. In a recent systematic review of vitamin B6 status in MHD patients, Corken and Porter [195] reported a 33%–56% prevalence of vitamin B6 deficiency when low plasma PLP was used as the criterion for deficiency. However, this was not observed in a small cohort of children undergoing CPD and MHD; even those children who were not receiving vitamin supplements or enteral feeding had normal vitamin B6 concentrations [196]. In an adult cohort of 68 CKD stages 2–5 patients, of whom 18% were receiving vitamin B supplements, and 68 MHD patients treated with high-flux membrane of whom 48% were taking vitamin B supplements, plasma PLP, measured by HPLC, was in the normal range in 88% of the CKD patients and 97% of the MHD patients [197]. Busch et al. [198] analyzed vitamin B6 status with HPLC measurements of PLP in 48 CKD 2–4 patients, 72 MHD patients, 38 kidney transplant patients, and 141 healthy subjects. The MHD patients had received 10 mg of pyridoxine HCl after each dialysis session, whereas controls and the other patients were not taking vitamin B6 supplements. The CKD and kidney transplant patients had higher levels of plasma and RBC PLP compared to controls despite the absence of supplementation. MHD patients displayed decreased plasma PLP but not RBC PLP. Most strikingly, the vitamin B6 metabolite, 4-PA, was very high in plasma and RBC of the MHD patients which was probably due to the loss of renal function and possibly metabolism of the supplemental pyridoxine HCl. There was no relationship between the vitamin B6 status in plasma or RBC and the history of CV events. The authors questioned whether the PA accumulation was safe, and indeed a subsequent report has associated high levels of plasma PA with tingling hands, diarrhea, and tachycardia in MHD patients who were taking large doses of pyridoxine HCl such as 50 mg/d [199].

The removal of vitamin B6 by HD was invoked to explain the low plasma PLP in MHD patients [198]. However, whether much vitamin B6 is removed by HD is not clearly established. Lacour et al. [200] did not find PLP in spent hemodialysate obtained from low-flux HD. This is not surprising since PLP is largely bound to albumin. The magnitude of PLP clearance with high-flux membranes is conflictory. Kasama et al. [201] observed a significant reduction in predialysis serum PLP in six MHD patients after they changed from cuprophane to cellulose triacetate dialyzer membranes, whereas Heinz et al. [153] did not find any difference in serum PLP with the same study design. No data are currently available on PLP clearances with convective techniques. Boeschoten and coworkers reported that the quantity of PLP lost into peritoneal dialysate, assessed by HPLC, is similar to the normal urinary excretion of vitamin B6 [32]. In another study, much lower losses of PLP were reported with peritoneal dialysis [202]. However, some additional PLP bound to proteins may be lost into peritoneal dialysate.

In 10 AKI patients treated for with continuous venovenous hemofiltration (CVVH) or hemodiafiltration, serum PLP decreased, and the calculated PLP loss was 80 nmol/day [203], the PLP clearance was about 49% of the urea clearance. In 75 AKI patients who were receiving Continuous Renal Replacement Therapy (CRRT) (mainly CVVH) with nutritional support, serum vitamin B6 was below the normal range in 67% of the patients [160].

Clinical significance of vitamin B6 deficiency in chronic kidney disease

As in the general population, there is no obvious clinical syndrome of vitamin B6 deficiency that has been described in CKD patients. However, several abnormalities that are common in vitamin B6 deficiency are often present in advanced CKD or chronic dialysis patients. In experimental animals and in humans, vitamin B6 deficiency is associated with many alterations in immune function, including reduced numbers of blood granulocytes and lymphocytes, decreased lymphocyte maturation, reduced blastogenic response of lymphocytes to mitogenic stimuli, delayed cutaneous hypersensitivity, and decreased antibody production. B6 deficiency may play a role in the alterations of immune function in advanced CKD. Many years ago, Dobbelstein et al. [204] were able to reverse decreased reactivity in mixed lymphocyte culture by giving MHD patients 300 mg/d of pyridoxine HCl for 2 weeks. Kopple et al. [205] found that a normal EGPT index of 1.25 or lower was maintained with much lower doses of supplemental pyridoxine HCl, 10 mg/d in MHD patients and 5 mg/d in advanced CKD and CAPD patients. Casciato et al. [206]

improved immunologic function of polymorphonuclear neutrophils and lymphocytes in eight MHD patients, most of whom had vitamin B6 deficiency, by giving 50 mg/d of pyridoxine hydrochloride for 3–5 weeks. Recently, Chen et al. [197] reported that plasma PLP and pyridoxal, alone or in combination, were negatively correlated with serum CRP and IL-1, supporting the link between vitamin B6 deficiency and inflammation in CKD. However, studies of the effects of vitamin B6 supplements on inflammatory markers in CKD patients are lacking. Vitamin B6 deficiency may also enhance the risk of oxalate formation and deposits (see the next paragraph and the section on vitamin C). In a randomized, blinded, prospective clinical trial in 26 MHD patients with symptoms of peripheral neuropathy, there was dramatic improvement of symptoms in 14 patients who received pyridoxine HCl, 60 mg/d, for 4 weeks, but not in 12 patients who received vitamin B12, 500 μg/d orally, even though the initial serum PLP was only slightly and not significantly lower than in controls [207]. However, no objective measurements of motor nerve conduction velocity were reported in this chapter.

Vitamin B6 and oxalate metabolism in chronic kidney disease

Oxalate is a known uremic toxin [208]. Oxalate is normally excreted in the urine. Very little oxalate is degraded in vivo in humans. Ascorbic acid contributes importantly to oxalate synthesis (see the section on vitamin C), and vitamin B6 deficiency also plays a key role. Pyridoxine is the coenzyme for the transamination of glyoxylate to glycine (Fig. 26.4). Vitamin B6 deficiency, which is not uncommon in CKD, may contribute to increased oxalate formation and plasma oxalate levels. Hence, both decreased removal of oxalate because of impaired renal function and reduced vitamin B6 activity may increase plasma oxalate. Mydlik et al. [209] reported a close relationship between the vitamin B6 nutriture and serum oxalate levels in MHD patients (Fig. 26.5). Several attempts have been made to decrease plasma oxalate levels with pharmacological doses of pyridoxine HCl. Conflicting results were obtained. Tomson et al. [210] did not observe a significant decrease in plasma oxalate in 21 chronic dialysis patients treated for 4 months with pyridoxine HCl, 100 mg/d. In contrast, a 46% decrease in plasma oxalate was observed by Balcke et al.

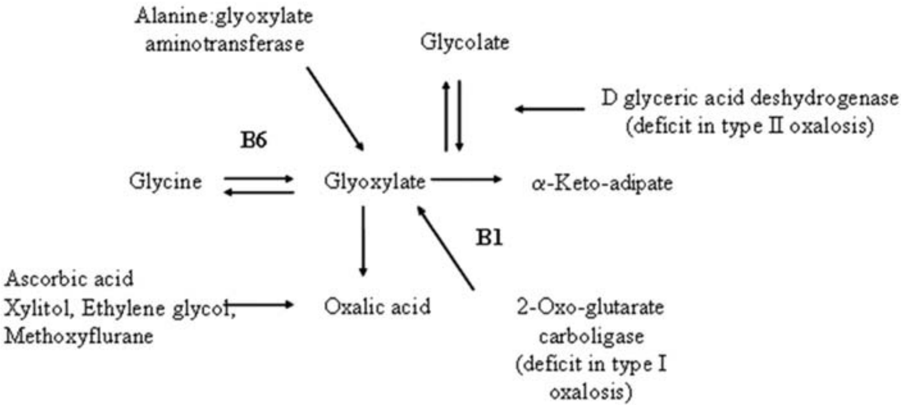
Alanine:glyoxylate aminotransferase
Glycolate
D glyceric acid deshydrogenase (deficit in type II oxalosis)
B6
Glycine
Glyoxylate
α-Keto-adipate
B1
Ascorbic acid
Xylitol, Ethylene glycol, Methoxyflurane
Oxalic acid
2-Oxo-glutarate carboligase (deficit in type I oxalosis)

FIGURE 26.4 Pathways for oxalate metabolism.

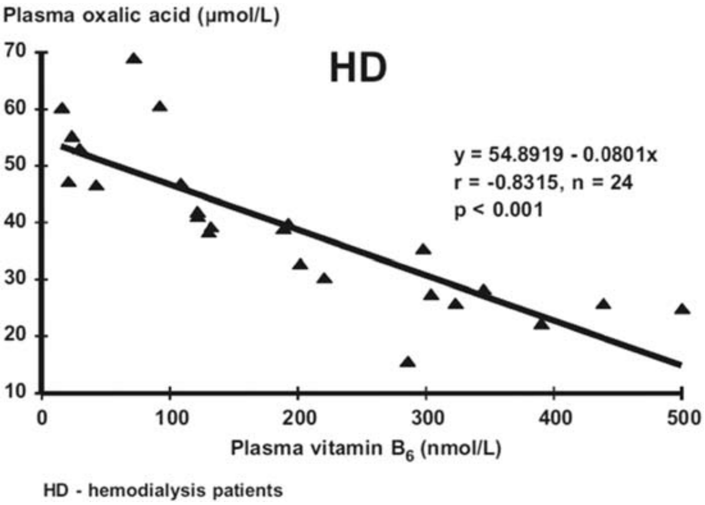

FIGURE 26.5 Negative relationship between plasma vitamin B6 concentrations and plasma oxalate concentrations in maintenance HD patients. *HD*, Hemodialysis. *Source: Mydlik M, Derzsiova K. Vitamin B6 and oxalic acid in clinical nephrology. J Ren Nutr 2010;20:S95–102. Reproduced with permission from the Editot.*

[211] in MHD patients after 1 month treatment with pyridoxine HCl, 600 mg/d orally or 600 mg three times per week intravenously after HD treatments. However, plasma oxalate levels remained elevated with treatment and in the supersaturation range as reported by Worcester et al. [212]. In a controlled but not randomized study, Costello et al. [213] were unable to reduce plasma oxalate levels after 6 months of treatment with 100 mg/d of pyridoxine HCl or after 4 weeks of therapy with 750 mg/d of pyridoxine HCl. The reason for these discrepant results is not clear. Descombes et al. [214] reported a high plasma oxalic acid level in 33 patients receiving high-flux dialysis and 50 mg of pyridoxine HCl after each dialysis treatment, indicating that current dialysis techniques and vitamin B6 supplementation are not sufficient to normalize plasma oxalic acid levels. Patients with type I or type II primary hyperoxaluria have been treated with various doses of pyridoxine (25−1000 mg/d), also with variable results [215]. Oxalate clearance with dialysis differs with different dialyzers and dialysis modalities; the most efficient ones are the high-flux membranes, such as polysulfone and hemodiafiltration [216]. Renal transplantation remains the most effective therapy for hyperoxalemia [217].

Vitamin B6 supplementation in advanced chronic kidney disease, chronic dialysis, and kidney transplant patients

Many workers in the field agree that there is a need for routine pyridoxine supplementation in CKD, MHD, CPD patients, and nephrotic patients. Recommended supplemental pyridoxine HCl doses vary from 1.2 mg/d [176] to 50 mg three times/wk [214]. These recommended doses were not based on dose−response studies, and, therefore, the daily vitamin need might differ from these recommendations. Kopple et al. [205], in a dose-finding study, found that a supplemental pyridoxine HCl dose of 10 mg/d, which is 82.3% pyridoxine, maintained a normal EGPT index of 1.25 or lower in all MHD patients. Lower daily pyridoxine HCl doses did not reliably maintain EGPT indexes at or below 1.25 in people undergoing MHD. When advanced CKD and CPD patients received a pyridoxine HCl supplement of 2.5 mg/d, the EGPT fell to normal slowly and often decreased to barely within the normal range. These findings suggest that CKD and CPD patients may need a pyridoxine HCl supplement of 5.0 mg/d (4.1 mg/d of the pyridoxine base) to ensure that they have a normal EGPT index. When sepsis is present or patients are taking medicines that are vitamin B6 antagonists, a supplemental pyridoxine HCl dose of 10 mg/d may be needed for CKD and CPD patients as well as MHD patients. This study was limited by the fact that sample sizes in many of the groups studied at a given dose were rather small [205]. In CAPD patients, Ross et al. found the lowest pyridoxine HCl dose that normalized serum PLP levels to be 10 mg/d [202]. Kopple et al. only studied the EGPT index as the indicator of B6 adequacy in these dose−response studies [205]. As indicated in this review, in CKD and chronic dialysis patients, various doses of pyridoxine HCl normalized one or more parameters of vitamin B6 status; and it would seem helpful to repeat these dose−response studies measuring, in addition to the EGPT or EGOT index, the actual vitamin B6 molecules in plasma as well as some of the other vitamin B6 function tests [206].

In eight children undergoing CPD, Kriley and Warady reported that 10 mg/d of pyridoxine HCl increased serum PLP to twice the normal control levels [218]; lower doses of pyridoxine HCl would probably be adequate for this pediatric population. It is important to remember that the pyridoxine HCl dose that engenders a normal serum PLP level or EGPT or EGOT index may not necessarily indicate the desirable daily dose. Such factors as synthesis inhibitors, altered binding or cellular transport, or discrepant intracellular concentrations, could alter the needed doses for vitamin B6 in renal failure. In the absence of evidence to the contrary, it seems sensible to accept normal plasma levels as an appropriate or criterion for determining the desirable daily vitamin B6 dose. In MHD patients, Mydlik et al. [219] recommended 20 mg/d of pyridoxine HCl to correct or prevent a decrease in RBC vitamin B6 levels that may occur after several months of EPO treatment. Again, this was not a dose−response study. By contrast, 60 mg of pyridoxine HCl after each dialysis session was associated with a decreased hematological response to EPO [220]. In renal transplant recipients, no pyridoxine dose studies have been conducted. Based on these foregoing data, we recommended a daily dose of 5 mg of pyridoxine HCl for nondialyzed CKD 3−5, CPD, and CKD T1−5 patients and 10 mg for MHD patients (Table 26.4). Vitamin B6 supplementation in CKD patients was addressed as with thiamine and riboflavin by the recent update of the KDOQI nutrition guidelines [1] and no routine vitamin B6 supplementation was recommended (Table 26.4). Vitamin B6 supplements have been recommended for AKI patients to prevent or treat B6 deficiency, especially in patients with AKI-2 and AKI-3 who have high illness scores and are receiving renal replacement therapy (see Chapter 35: Metabolic Management and Nutritional Support in Acute Kidney Injury).

Vitamin B6 has been given as piridoxilate, which is a vasodilator that has been used to treat coronary artery and peripheral circulatory insufficiency. This medicine can cause oxalate nephropathy and ESRD [221]. Very high doses of pyridoxine HCl (i.e., 200−600 mg/d) occasionally have been associated with peripheral neuropathy in patients without kidney disease [222]. Since advanced CKD patients have impaired ability to excrete metabolites of vitamin B6, it is possible that these metabolites might accumulate and interfere with the normal, active metabolites of vitamin B6. Indeed, 4-PA, the main metabolite of vitamin B6, is excreted primarily in the urine and might be expected to accumulate in patients with kidney failure, particularly in those taking vitamin B6 supplements. Therefore until more information is available, caution should be exercised when prescribing very large doses of pyridoxine HCl to nondialyzed CKD and maintenance dialysis patients (perhaps 25–50 mg/d or greater) for extended periods of time.

Summary:

- Vitamin B6 deficiency is often observed in advanced CKD and chronic dialysis patients.
- Dietary vitamin B6 intake is often below the RDA in advanced CKD and chronic dialysis patients.
- Many but not all studies indicate that vitamin B6 deficiency, determined by serum or blood measurements, is not uncommon in advanced CKD and chronic dialysis patients who are not receiving vitamin B6 supplements.
- Vitamin B6 deficiency is difficult to identify from clinical symptoms.
- Vitamin B6 deficiency may engender inflammation, immune dysfunction, increased oxalate generation, and polyneuropathy.
- Vitamin B6 supplements have been recommended for AKI-2 and AKI-3 patients to prevent or treat vitamin B6 deficiency which is often present, especially if they have high illness scores and are receiving dialysis treatment.
- The quantity of dietary vitamin B6 and supplemental pyridoxine HCl necessary to prevent or correct vitamin B6 deficiency from dose–response studies appears to be greater than the RDA for vitamin B6 in normal individuals.
- Since advanced CKD, MHD, and CPD patients commonly show evidence for vitamin B6 deficiency by laboratory testing, and their daily vitamin B6 requirement appears to be greater than normal, it is recommended that these patients should be given routine supplements of pyridoxine HCl.
- Vitamin B6 supplements should be given as pyridoxine HCl, 5 mg/d for nondialyzed advanced CKD and CPD patients and 10 mg/d for MHD patients.

Vitamin C (ascorbic acid), physiology, biochemistry, and nutritional status in chronic kidney disease patients

Vitamin C physiology and biochemistry

Vitamin C (ascorbic acid, Table 26.1) deficiency can cause scurvy. Vitamin C is oxidized to dehydroascorbic acid (DHAA) which possesses antiscorbutic activity. Ascorbic acid is mainly found in fresh fruits (e.g., blackcurrant, strawberry, lemon, orange, and lime) and vegetables (e.g., broccoli, Brussels sprouts, cauliflower, and cabbage). Ascorbic acid in food can be degraded by heat or extracted in cooking water. Absorption of ascorbic acid is an active, energy-requiring, and saturable process in the proximal part of the small intestine. About 70%–90% of the usual dietary vitamin C intake is absorbed in the intestine, but this fraction decreases substantially when large loads of ascorbic acid are ingested. In plasma, vitamin C is not protein-bound and is present in a reduced form. Ascorbic acid enters the cell by active transport. The average half-life of ascorbic acid in normal adult humans is about 16–20 days. The body ascorbic acid pools are regulated by intestinal absorption, glomerular filtration, renal tubule reabsorption, and catabolism of this vitamin [223]. Excess ascorbic acid is filtered at the glomerulus and excreted intact in the urine. The catabolic rate for ascorbic acid is directly related to the body pool size. Ascorbic acid can be oxidized to DHAA and then to a variety of compounds, including L-xylose, threonic acid, and oxalic acid that are excreted in urine. Oxalic acid constitutes 5%–10% of the ascorbic acid metabolites. The methods for measuring ascorbic acid have evolved from colorimetric methods, based on the reductive properties of ascorbic acid, to HPLC technology that is sensitive and specific [224]. The oxidized form of ascorbic acid, the ascorbyl free radical, can be detected by electron paramagnetic resonance spectroscopy. Ascorbic acid can be measured in plasma, which reflects recent dietary intake, and in leukocytes, which gives a more accurate estimate of the total body pool of ascorbic acid. Women usually have higher plasma ascorbic acid levels than men; smokers and elderly individuals have lower plasma ascorbic acid values. The function of ascorbic acid is largely due to its reversible reducing power. For instance, ascorbic acid plays an important role in metal-catalyzed hydroxylations by reducing the metal catalyst and allowing the metal–enzyme complex to reconstitute after it is oxidized. Perhaps the most well-recognized activities of ascorbic acid are collagen synthesis via lysyl and prolyl hydroxylations, hydroxylation of peptidyl proline, and enhanced secretion of procollagen that contains hydroxyproline. Ascorbic acid is also important for carnitine synthesis, for hydroxylation of dopamine to form norepinephrine, for hydroxylation of tryptophan to form serotonin, and also for amidation of peptide hormones, intestinal iron absorption, and antioxidant protection of folate and vitamin E. Several medications may interfere with vitamin C metabolism or actions. These are summarized in Table 26.2.

Dietary vitamin C (ascorbic acid) intake in chronic kidney disease patients

Farhadnejad et al. [14] studied the incidence of CKD and its relationship to nutrient intake for 3.6 years in a large cohort of healthy subjects without CKD. The upper quintiles of the dietary intake vitamin C, as well as folates, vitamins B12 and E, magnesium, and potassium, were associated with a significantly lower incidence of CKD during the follow-up, which is opposite to the increased incidence of CKD in patients in the higher quintiles of sodium intake. Asghari et al. [225], in 1179 subjects with glucose intolerance who were followed for 3 years, found that the upper tertiles of dietary total antioxidant capacity and vitamin C intake were associated with a 40% lower incidence of CKD. Vitamin C intake in CKD patients has been more extensively studied than most other micronutrients. Dietary vitamin C is reported to be inversely correlated with protein intake (Table 26.3; [15]). In the early days of chronic dialysis treatment, the average ascorbic acid intake of MHD patients was reported by Sullivan et al. [226] to be 34 mg/d, whereas the RDAs for ascorbic acid are, respectively, 75 and 90 mg/d in normal nonsmoking female and male adults [48]. Allman et al. [176] showed a low spontaneous intake of vitamin C in their MHD patients (69% consumed less than two-thirds of the RDA). More recently, in an Italian cohort of adult MHD patients, vitamin C intake was found to be below the RDI in almost all patients [3]. Chan et al. [16] identified insufficient intakes for vitamin C in 22% of 210 CKD stages 4—5 patients. Jankowska et al. [4] reported low vitamin C intakes, below the DRI, in 48%, 67%, 55%, and 52% of nondialyzed advanced CKD, MHD, CPD, and kidney transplant patients, respectively. These findings of frequent low ascorbic acid intake in a large proportion of kidney transplant patients are in contradiction with Bohm et al. [227] who found that renal transplant recipients have a vitamin C intake equal to the RDA. Regarding CPD patients, the high prevalence of low vitamin C intake observed by Jankowska et al. [4] is similar to previous reports [17,18]. In children undergoing MHD and CPD, vitamin C intake was found to be 51% and 77% of the RDA, respectively [228].

Today, because low-potassium diets, which typically are also low in ascorbic acid containing fruits and vegetables, are frequently prescribed for advanced nondialyzed CKD and chronic dialysis patients, the intake of vitamin C—containing foods is likely to be reduced. Hence, restriction of foods high in potassium commonly reduces the intake of ascorbic acid and may predispose to vitamin C deficiency [229]. Among the prescribed restrictions in dietary intake for chronic dialysis patients, the reduction in potassium is the one most likely to be adhered to [230], and this increases the risk of low vitamin C intake. Moreover, prolonged soaking and boiling of vegetables, which may be employed to reduce the potassium content of food, may leech out or degrade ascorbic acid. Hence, ingesting the RDA for vitamins will depend on many factors, including the dietary prescription and the patient's adherence to the prescription, appetite, medicinal intake (see Table 26.3) and superimposed illnesses (see next). As recommended in the KDOQI CPGs for nutrition in CKD: 2020 update [1], a registered dietitian nutritionist or an international equivalent is the key person to evaluate the nutritional intake and status of the CKD and ESRD patients. This person should alert the patient and the nephrologist if the patient's vitamin needs are not being met.

Vitamin C nutritional status in advanced chronic kidney disease, chronic dialysis, kidney transplant, and acute kidney injury patients

Advanced CKD and nephrotic patients are usually reported to have lower serum vitamin C levels as compared to healthy controls. Rajbala et al. [231] found decreased serum vitamin C in 45 children presenting with the nephrotic syndrome. This was confirmed by Fydryk et al. [232] who found decreased blood vitamin C during relapse of steroid-dependent nephrotic syndrome in 18 children. Vitamin C and E status were studied in 29 nephrotic patients and compared to 25 patients with hematuria [233]. Plasma vitamin C and the plasma ascorbate/vitamin E ratio were significantly lower in the nephrotic patients. Marumo [184] surprisingly found low plasma ascorbic acid levels in patients with mild-to-moderate CKD but not in nondialyzed advanced CKD patients or MHD patients. In contrast, Clermont et al. [59] found decreased plasma vitamin C levels with an increased ascorbyl-free radical/ascorbic acid ratio in advanced CKD patients. Intravenous furosemide increases urinary vitamin C excretion in CKD patients [234]. Gillis et al. [235] reported significantly lower plasma ascorbic acid levels, measured by HPLC, in 30 CKD stages 3—5 patients (average eGFR = 22.4 ± 12.6 mL/min/1.73 m^2) compared to 20 hypertensive subjects without CKD. Bohm et al. [227] reported normal plasma vitamin C concentrations in renal transplant recipients. In 51 nonvitamin supplemented CKD stages 3—5 patients and 50 MHD patients, compared to 38 healthy controls, Gondouin et al. [236] found significantly lower plasma ascorbic acid levels, assessed by HPLC, in the CKD patients as compared to the controls. The MHD patients had significantly lower vitamin C plasma levels then the CKD patients.

In the early days of MHD treatment, Sullivan and Eisenstein described ascorbic acid deficiency in MHD patients [226]. Later reports confirmed a high prevalence of vitamin C deficiency in MHD and CPD patients who were not given vitamin C supplements [32,59,158,176,237,238] and even in some patients receiving such supplements [152]. However, Tarng et al. [239] found normal vitamin C levels in 65 nonsupplemented patients who had undergone MHD for a mean of 48.7 months. Ramirez et al. [148] monitored plasma ascorbic acid levels in MHD patients for 1 year after discontinuing vitamin C supplements. A dramatic decrease in plasma ascorbic acid was observed, but no patient reached a deficient level. Mydlik et al. [240] found normal plasma vitamin C levels in 32 CAPD patients not receiving ascorbic acid supplements. More recently, Zhang et al. [241] reported that 64% of 284 MHD and CAPD patients manifested deficiency or insufficiency for vitamin C, as determined by low plasma ascorbic acid levels. Sirover et al. [242] determined that 38% of a cohort 203 MHD patients had plasma acid ascorbic values, measured by HPLC, below 30 μmol/L, which is below normal levels, even though 52% of the patients were prescribed vitamin C supplements Importantly, Deicher et al. [243] studied the relationship between acid ascorbic level and the occurrence of adverse cardiovascular events (MACE) and mortality in 138 prevalent HD patients during a 30-month follow-up period. Lower (< 32 μMoles/L) and middle (32−6 μMoles/L) tertiles of vitamin C were significantly associated with MACE and CV mortality when compared to the group of patients in the upper tertile of vitamin C.

Ascorbic acid is a small MW, nonprotein-bound molecule, which is readily dialyzable. Bohm et al. [227] measured the amount of vitamin C in dialysate and found it to range from 92 to 334 mg per treatment; there was a 50% decrease in plasma ascorbic acid during an individual HD treatment and a return to predialysis levels by 44 hours. Hultqvist et al. [237] found a 40% decrease in plasma ascorbic acid during a 3-hour HD treatment. More recently, Sirover et al. [242] reported a 60% decrease of ascorbic acid in eight patients between the start and end of an HD session. Morena et al. [244] studied the effect of convection on vitamin C losses during paired-filtration. On average, 19 MHD patients lost 66 mg of ascorbic acid during the hemodiafiltration session, with one-third of these losses related to convection. Concerning peritoneal dialysate, 56 mg of ascorbic acid were recovered during a 24-hour PD cycle [32]. According to Mydlik et al. [240], the peritoneal transfer of ascorbic acid is affected by the dialysate glucose concentration. Ascorbic acid losses into peritoneal dialysate during CAPD were 136.4 μmol during 6 hours of PD with 1.5% glucose in dialysate, and 175.8 μmol during 6 hours of PD with 2.5% dialysate glucose. These impressive decreases in plasma ascorbic acid during HD and the substantial recoveries of ascorbic acid from hemodialysate and peritoneal dialysate probably reflect the fact that ascorbic acid is not protein-bound in plasma and that normal plasma ascorbic concentrations tend to be high in comparison to other vitamins. In 75 AKI patients who were receiving CRRT (mainly CVVH) with nutritional support, serum vitamin C levels were below the normal range in 80% of the patients [160].

Scurvy in chronic kidney disease patients

The foregoing data indicate that low plasma ascorbic acid levels are common in MHD and CPD patients who do not receive vitamin C supplements, but scurvy is seldom described in these patients. Ihle and Gillies reported a case of scurvy in an MHD patient in 1983 [245]. The patient manifested cutaneous symptoms (pruritus, bruising, and ecchymoses), impaired platelet function, a low vitamin C intake, and decreased plasma and leukocyte ascorbic acid levels. The defect in platelet function was similar to that reported with scurvy. Treatment with 1 g of vitamin C per day for a few days rapidly corrected the ecchymoses, prolonged bleeding time, and platelet dysfunction. Fatigue and periodontal lesions are frequent in dialysis patients, and their relationship to the frequent occurrence of vitamin C deficiency had not been thoroughly addressed until a few years ago [246]. Raimann et al. [247] reported a significantly higher prevalence of periodontal disease and teeth losses in MHD patients with serum ascorbic acid levels <10 μmol/L compared to patients with serum ascorbic acid above this level. More recently, scurvy has been occasionally described in both MHD and CPD patients [248−250].

The oxalate burden in chronic kidney disease

As shown in Fig. 26.4, oxalate is a metabolic end product of ascorbic acid. It is an admitted uremic toxin [208] (see also the section on vitamin B6). In normal humans, urinary excretion of oxalate increases when they are fed an ascorbic acid load. However, the relationship between ascorbic acid intake and urinary oxalate excretion is not linear, and only a fraction of the ascorbic acid ingested is normally recovered in the urine as oxalate [251]. Recently, increased urinary oxalate excretion has been identified as an independent risk factor for CKD progression in CKD stages 2−4 [252]. Plasma oxalate concentrations are almost always increased in nondialyzed advanced CKD and chronic dialysis patients [212,253]. The increase in plasma oxalate becomes statistically significant when GFR falls below 30 mL/min [254]. In kidney transplant recipients who underwent kidney biopsies during the first 3 months after transplantation, Kelly et al. [255] observed oxalate crystal deposits in 19.4% of the grafts. Higher serum creatinine, diabetes mellitus, and dialysis vintage were associated with these oxalate deposits. Plasma oxalate is correlated with serum creatinine [217] and may be increased several times above normal values in chronic renal failure patients—and close to the levels found in primary hyperoxaluria. Calcium oxalate deposits are described in several tissues in advanced CKD patients and appear to be most pronounced in kidneys, heart, blood vessels, thyroid gland, and skin and to increase with the duration of MHD therapy [256]. Mydlik et al. [240] reported increased plasma oxalic acid in 32 CAPD patients [23.6 ± 7.4 μmol/L (SD); normal range, 2−5.5 μmol/L] even though these patients displayed a large peritoneal clearance of oxalate. In 15 MHD patients who also had increased plasma oxalate [40.3 ± 9.8 μmol/L (SD)], oxalate clearance was greater with postdilutional hemofiltration (oxalate clearance, 74.2% of urea clearance) than with conventional HD (oxalate clearance, 58.1% of urea clearance) or postdilutional hemodiafiltration (oxalate clearance, 69% of urea clearance) [257]. In children, there appears a large discrepancy between dialysis oxalate clearances in those undergoing CAPD (7.14 mL/min, $n = 15$) and MHD (115.6 mL/min, $n = 10$). Nonetheless, because CAPD is conducted almost continuously, whereas MHD is performed for only about 12 h/week, the weekly elimination of oxalate was similar with these two treatments, and blood oxalic acid levels remained high and not different between the two groups [258]. A serum oxalate level >30 μmol/L has been proposed as the threshold that indicates calcium oxalate supersaturation in plasma [259].

There is strong evidence that a high vitamin C intake may contribute to hyperoxalemia and oxalate deposition in soft tissues of CKD patients. Oxalate accumulation with even low doses of ascorbic acid is related to the reduced GFR. With increased intake of ascorbic acid, the oxalate subsequently produced cannot readily be excreted in urine. Unlike in normal individuals who can tolerate much higher intakes of ascorbic acid without oxalate accumulation, the oxalate levels in advanced CKD and chronic dialysis patients will increase with these doses. In MHD patients, plasma oxalate levels increased with oral supplementation of 0.5−1 g/d of ascorbic acid; cessation of ascorbic acid supplements resulted in a decrease in plasma oxalate [260]. The calcium oxalate saturation threshold was exceeded in 7 of 18 patients (40%) during the course of 6 months of ascorbic acid therapy, 500 mg/week [261]. Ott et al. [262] observed bone oxalate deposits in a bone biopsy from a patient who had undergone MHD for 23 years and who had ingested 2.6 g/d of ascorbic acid for 7 years. A bone biopsy in the same patient obtained before commencing ascorbic acid supplements showed no evidence of bone oxalate deposits. Calcium oxalate deposits in kidneys and pancreas was reported in a pediatric patient with the hemolytic uremic syndrome (HUS) who received 500 mg/d of ascorbic acid by parenteral nutrition for 3 months [263]. Hyperoxalemia is also associated with ascorbic acid supplementation in CPD patients [264]. Severe oxalate crystal deposits were found in the retina associated with proliferative retinopathy in a nondiabetic CPD patient who was taking over-the-counter purchased ascorbic acid, 4 g/d [265]. The patient's serum oxalate was 187 μmol/L (normal serum oxalate, <1.7 μmol/L). Certain types of bariatric surgery with gastric bypass procedures present a risk for increased intestinal oxalate absorption, and higher vitamin C intakes in this context may trigger oxalate nephropathy [266]. The role of vitamin B6 deficiency and sufficiency in oxalate metabolism is described in the section on vitamin B6.

Vitamin C and anemia management in chronic kidney disease

The high prevalence of erythropoiesis stimulating agent (ESA) resistance, especially of inflammatory origin, and the quest to reduce the costs of ESA therapy for nondialyzed advanced CKD and chronic dialysis patients have led to many studies to improve the hemopoietic response to ESA. Since ascorbic acid ingestion enhances the intestinal absorption of iron, there is much interest concerning the potential value of ascorbic acid as adjuvant therapy to ESA particularly in MHD and CPD patients who have EPO-resistant anemia. Tarng et al. [239] reported that in MHD patients who were hyporesponsive to ESA, had normal plasma vitamin C levels, and were treated with 300 mg of vitamin C given at the end of each dialysis session for 8 weeks, the hematocrit and transferrin saturation increased, even though the dosage of ESA decreased. However, only one-half of these patients had a positive response to vitamin C treatment. From the receiver operating characteristic analysis, the predictors of response to vitamin C were a combination of transferrin saturation below 25% and erythrocyte-zinc protoporphyrin level above 105 mmol/mol heme. Plasma oxalate levels increased slightly, but not to a statistically significant degree during vitamin C therapy. In past decades, many studies have indicated that vitamin C administration reduces anemia in renal failure. A metaanalysis identified 157 reports, but only six of these reports fulfilled the selection criteria for critical analysis [267]. The authors concluded that vitamin C, between 200 and 500 mg three times per week, increases the transferrin saturation coefficient and decreases ESA needs. However, the long-term safety of such treatment was not addressed in this report, and oxalate supersaturation might have been reached in significant numbers of patients with these dosages [261]. In another metaanalysis for therapy of ESA resistance, only two studies met the selection criteria and showed a lack of benefit of vitamin C supplements. The KDIGO guidelines on anemia management do not recommend such adjuvants as folates or vitamin C with ESA therapy [268]. See also Chapter 38, Nutrition and Anemia in Chronic Kidney Disease.

Vitamin C, inflammation, oxidant stress, and endothelial dysfunction in chronic kidney disease

In a crossover study, Zhang et al. [269] reported a significant decrease in plasma high-sensitivity CRP and a significant increase in plasma prealbumin after 3 months of vitamin C supplementation in 100 MHD patients, whereas serum albumin, hemoglobin, and the EPO-resistance index did not change. After vitamin C was stopped, plasma CRP and prealbumin returned to the initial levels. In a randomized double-blind trial in 151 MHD patients, Biniaz et al. [270] observed a significant reduction in serum CRP in the treated patients who were given 250 mg of ascorbic acid intravenously thrice-weekly. Morena et al. [244] found markers of oxidant stress to be significantly higher in MHD patients as compared to healthy subjects. The authors attributed the increased oxidant stress to significantly lower plasma vitamin C concentrations and the vitamin C losses during HD. Vitamin E could not account for these differences, because the vitamin E levels were not different between the two groups. Other studies with supplemental vitamin C show conflicting results with regard to effects on the patients' oxidation status, and no study of vitamin C supplements has addressed clinical outcomes of the patients. Interesting data have been published indicating beneficial effects of vitamin C on endothelial dysfunction that occurs not uncommonly in advanced CKD patients [271]. A study in patients with advanced CKD who were not receiving dialysis (mean GFR, 22 mL/min/1.73 m^2) found low plasma vitamin C levels as compared to 30 hypertensive patients with normal GFR [235]. One single large intravenous dose of vitamin C (2000 mg) significantly reduced ADMA in the patients with advanced CKD, but not in the patients with hypertension. Central blood pressure decreased in both groups, but the flow-mediated dilation (FMD) did not. In children with CKD who were receiving a daily dose of vitamin C, 250 mg/d, the carotid intima−media thickness decreased significantly, but FMD did not change [272]. Also, in a metaanalysis, including 19 trials, the relative risk of radiocontrast-induce nephritis (CIN) was reduced to 0.69 (95% CI, 0.49−0.82; $P = .0005$) by adding vitamin C versus saline [80]. However, vitamin C alone or combined with *N*-acetylcysteine was not more effective at preventing CIN than *N*-acetylcysteine alone. These data concerning endothelial dysfunction and vitamin C treatment are encouraging. But the safety of such large doses of vitamin C, particularly with regard to the risk of hyperoxalemia and acidemia, needs to be established before such doses can be recommended.

Vitamin C in critically ill patients

The association of vitamin C, thiamine, and steroids (ATS) has been recently studied in critically ill patients. See also the discussion on vitamin B1 (thiamine) earlier. The use of vitamin C per se in intensive care and cardiac surgery has been analyzed in a recent metaanalysis that was inconclusive regarding its benefit [273]. It is also questionable whether such high doses of acid ascorbic are safe. A case of oxalate nephropathy has been reported in a woman hospitalized with severe burns who received 101 g of vitamin C intravenously in 18 hours [274]. She died with AKI and lactic acidosis, and her autopsy confirmed oxalate nephropathy. In another case a 57-year-old woman who was in septic shock due to legionella pneumonia developed AKI was treated with CRRT. A kidney biopsy was performed after 72 days of persistent anuria, and oxalate nephropathy was identified [275]. The cumulative dose of vitamin C that she had received was 30 g over 2.5 months, which is much closer to what is recommended for ATS therapy.

Vitamin C supplementation in advanced chronic kidney disease, chronic dialysis, and kidney transplant patients

Many studies suggest that MHD and CPD patients are at risk for vitamin C deficiency if they do not take additional ascorbic acid, and various amounts of daily ascorbic acid supplements have been recommended. The combination of insufficient dietary intake and dialysate losses of vitamin C appears to be the cause of deficiency. Foods that are rich in vitamin C are often proscribed because of the high potassium content. There is no clear evidence that the dietary vitamin C requirement or the amount necessary to maintain normal plasma ascorbic acid levels is increased in chronic dialysis patients. Indeed, the lack of urinary vitamin C excretion will to some extent offset the dialysate losses. On the other hand, larger doses of vitamin C have been associated with increased oxalate concentrations in plasma and possibly soft tissues. It is possible that the ascorbic acid clearance with high-efficiency and/or high-flux hemodialyzers increases the dietary requirement for vitamin C. However, considering the small size of ascorbic acid (MW, 176), it is not likely that highly permeable dialyzers will markedly increase dialysis losses of vitamin C. At the present time, it is recommended that nondialyzed CKD 3–5, MHD, CPD, and kidney transplant patients be prescribed the RDA for ascorbic acid for nonpregnant, nonlactating adults, which is 75 mg/d for women and 90 mg/d for men (Table 26.4). This recommendation is consistent with the recent KDOQI nutrition in CKD guidelines, except that because low vitamin C intake is so prevalent and low serum vitamin C concentrations are so common, we recommend that the RDA for ascorbic acid be routinely supplemented to advanced CKD, MHD, and CPD patients [1] (Table 26.4). The low dietary vitamin C intakes in kidney transplant patients suggest that they should either be given supplemental vitamin C or monitored closely for vitamin C deficiency.

Summary:

- Vitamin C deficiency, as indicated by low plasma ascorbic acid concentrations, is very common in advanced CKD and chronic dialysis patients who do not take vitamin C supplements. Association with hard outcomes in HD patients has been reported.
- Low vitamin C intake, which is at least partly due to the need for CKD patients to eat potassium-restricted diets, and the losses of ascorbic acid during the dialysis procedure appear to be major contributors to the high prevalence of vitamin C deficiency in these individuals.
- Scurvy is infrequently described in CKD patients, but the long-term effects of subclinical vitamin C deficiency in CKD patients are unknown.
- Although some but not all reports have been encouraging reports, vitamin C supplements are not part of the KDIGO recommendations for anemia management for CKD patients who are receiving erythropoiesis stimulating agents.
- Whether ascorbic acid has antiinflammatory and antioxidant effects and may improve endothelial dysfunction in CKD and chronic dialysis patients requires more research.
- Critically ill patients with AKI often have low serum levels of vitamin C.
- The treatment of acutely and severely ill patients with vitamin C or a combination of vitamin C, thiamine, and glucocorticosteroids (ATS) to prevent or limit the severity of AKI and to decrease mortality remains controversial.
- Vitamin C may be effective for preventing CIN.
- Large doses of vitamin C may induce oxalate nephropathy and provoke AKI.
- Vitamin C supplements with 75 mg (women) and 90 mg (men) are recommended for nondialyzed advanced CKD, MHD, and CPD patients because of the restricted potassium diet and the losses of ascorbic acid during the dialysis procedure.
- Large doses of vitamin C should be avoided in CKD, chronic dialysis, and AKI patients because of the risk of oxalic acid toxicity.

Folate (vitamin B9), physiology, biochemistry, and nutritional status in chronic kidney disease patients

Folate physiology and biochemistry

Folate refers to a family of structurally related compounds that have pteroylglutamic acid at its core and serve major metabolic functions in the acceptance, redox processing, and transfer of one carbon (including methyl, formyl, methylene, and methenyl groups). Folic acid, which is pteroylmonoglutamic acid, is seldom found in nature or in food form, but because it is chemically stable and inexpensive, it is commercially synthesized and used as a vitamin supplement and as a fortificant in foods. Pteroylglutamic acid is composed of three subunits: a pteridine moiety, para-aminobenzoic acid, and glutamic acid (Table 26.1). Most naturally occurring food folates are pteroylpolyglutamates that contain from one to six additional glutamates that are joined to the gamma-carboxyl of glutamate. Reduced forms of folic acid are present both in foods and in the human body, usually as tetrahydrofolate (THF). Folates are found in many foods, including yeast, liver, meats, green vegetables, and fruits. Very sensitive to oxidation, folates are readily destroyed by extensive cooking and by food processing such as canning or refining [276]. Intestinal absorption occurs mainly in the proximal one-third of the small intestine. Polyglutamates require the action of conjugases, present in the brush border of enterocytes, to be transformed to folate monoglutamates, such as 5-methyl-THF, formyl-THF, or dihydrofolates. Another enzyme, the glutamate carboxypeptidase II anchored in the intestinal brush border, participates in polyglutamate catabolism. Devlin et al. [277] identified an H475Y DNA variant coding for this enzyme; low folate levels and hyperhomocysteinemia are associated with a 53% reduction of the enzyme activity. Cellular transport relies on specific folate membrane receptors, carriers, and cellular exit pumps. Folates are stored in the body as polyglutamates and require the action of conjugases, which are present in many tissues, to yield the biologically active monoglutamate form. However, polyglutamates may have physiological actions themselves. Actions of conjugases can be inhibited by various substances, including medicines. Indeed, many medicines may inhibit the actions of folate, including ones that are commonly prescribed for CKD patients (Table 26.2).

Folate in plasma is mainly free or loosely bound to nonspecific carriers. Delivery of folate to tissues requires a specific cell membrane receptor protein. Also, vitamin B12, which like folate is involved in transmethylation reactions, is necessary for cellular transport and storage of folate. Excretion of free folate and metabolites of folic acid occurs in urine and bile. A folate enterohepatic cycle helps to preserve the body pool of folates and is impaired by alcohol consumption. Folate nutriture is assessed mainly by measuring serum, plasma, or red cell folate levels with competitive binding protein assays that can detect nanogram quantities of 5-methyl-THF [278].

The fundamental action of folate can be summarized as one-carbon unit transfers [276]. Folic acid is required for DNA synthesis. The 5,10-methylene THF [requiring the vitamin B12–dependent transmethylation of homocysteine (Hcy)–methionine] delivers its methyl group to deoxyuridylate, which is transformed to thymidylate and is necessary for DNA synthesis. A defect in this step in DNA synthesis leads to megaloblastosis, which occurs in all replicating cells in the body but is most striking in bone marrow cells. Folate plays a role in amino acid metabolism, particularly for those amino acids that are methyl donors or receivers, including the interconversion of glycine and serine, the transformation of Hcy to methionine (Fig. 26.6), and the conversion of histidine to glutamic acid. Moreover, folate is required for purine synthesis in the methylation of transfer RNA. Unlike vitamin B12, folate is not involved in myelin synthesis, and, therefore, folate deficiency does not cause neurological disease.

Dietary folate intake in chronic kidney disease

The relationship between CKD and folate intake is complicated, because food fortification programs have been implemented in a majority of western countries, and it, therefore, is hard to both assess dietary folate intakes in different populations and to compare the differences in folate intake from peoples who do and do not receive folate fortification. As indicated earlier, Farhadnejad et al.

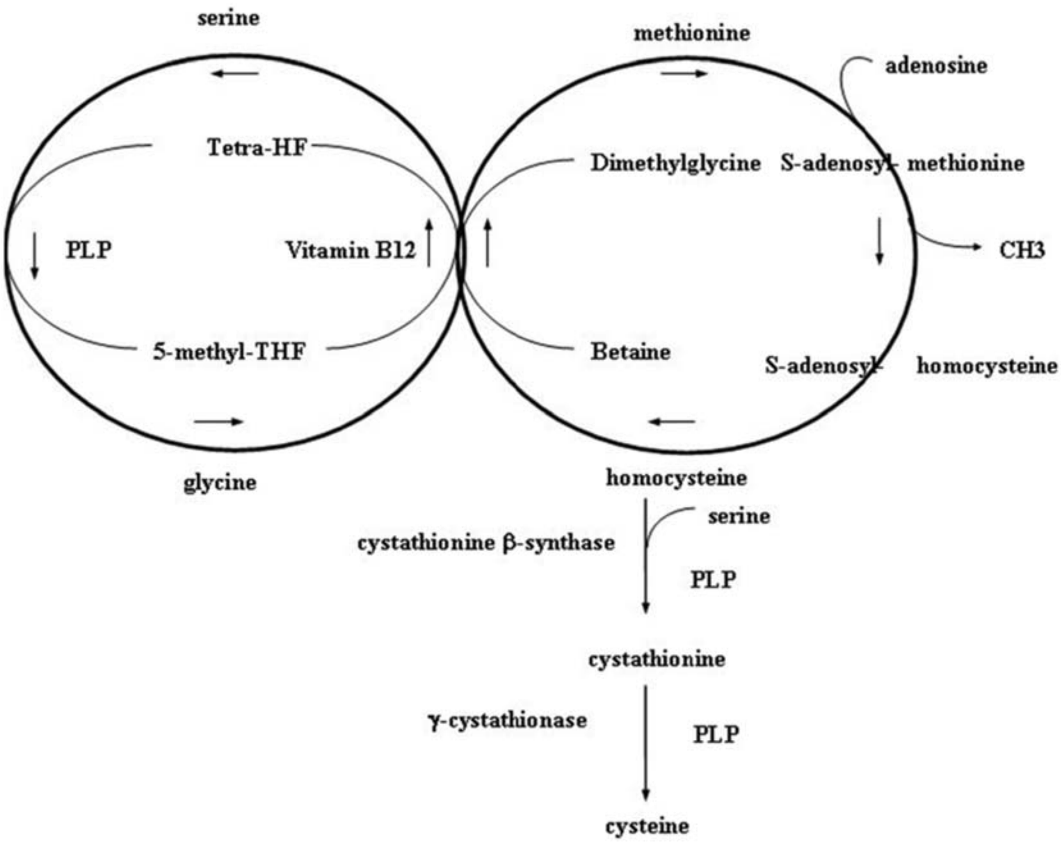

FIGURE 26.6 Role of folic acid, vitamin B12 and B6 in methionine–homocysteine–cysteine metabolism.

[14] reported that in a large cohort of healthy subjects followed for 3.6 years, the incidence of CKD was significantly lower in patients who were in the upper quintile of folate intake. The patients with a lower CKD incidence were also in the upper quintiles for vitamins C, B12, and E and magnesium and potassium intake. Dietary folate tends to be low with the protein-restricted diets commonly prescribed for nondialyzed CKD patients (Table 26.3; [15]). Hassan et al. [279] reported a direct relationship between daily folate intake and both the GFR and the potassium intake, which is also commonly reduced in advanced CKD patients. In a large cohort of CKD stages 4–5 patients, Chan et al. [16] found that folate intake was below the RDA recommendations in 68% of the patients. A high prevalence of low folate intake in 72% of these patients was confirmed by Jankowska et al. [4]. In this latter study, folate intake was also analyzed in MHD, CPD, and kidney transplant patients, and it was found to be below the EAR in 84%, 92%, and 77% of these individuals, respectively. Folate intake is reported to be inadequate in most CPD patients [17,18] and especially in those patients with little or no RRF and/or low peritoneal urea clearance [17].

Folate nutrition in advanced chronic kidney disease, chronic dialysis, kidney transplant, and acute kidney injury patients

Bayer et al. [280] unexpectedly found low serum folic acid levels in 44% of 31 patients who had secondary thrombotic microangiopathies without obvious cause. The significance of this finding is not known according to the authors. Folic acid metabolism is altered in renal failure. The intestinal absorption of THF is impaired in experimental animals with advanced CKD. Said et al. [281] showed that azotemic rats had significantly lower absorption of 5-methylTHF than sham-operated controls. Using the technique of perfusing an in vivo everted jejunal sac, these authors found that predialysis sera obtained from MHD patients suppressed intestinal absorption of 5-methylTHF, whereas postdialysis sera caused significantly less suppression. In rats with chronic kidney failure, Bukhari et al. [145] demonstrated downregulation of folic acid transporters in tissues, especially in the intestine. This could decrease intestinal folate absorption. Livant et al. [282] reported that plasma conjugase activity was reduced in predialysis sera and rose to normal levels after the HD session. The authors suggest that there are one or more circulating heat stable compounds in uremic plasma which may inhibit plasma folate conjugase activity. Moreover, significantly decreased folate receptor 2 (FR2) expression on mononuclear cell membranes has been described in 41 MHD patients compared to 21 healthy controls [283]. This finding is a bit puzzling because the FR2 mRNA was found to be increased and because high plasma Hcy levels, usually present in MHD patients, stimulate FR2 expression. Supplementation with folate decreased the FR2 mRNA but had no effect on the FR2 expression at the cell membrane. The authors conclude that reduced FR2 expression on cell membranes is one of the causes of folate resistance in advanced CKD patients [283].

Marumo et al. [184] reported that in CKD patients who were not receiving folate supplements, serum folate was normal in those with mild-to-moderate CKD and was increased above normal in advanced CKD patients who were not undergoing MHD. In the 1960–80s, reports regarding folate status in MHD patients were contradictory, and both normal and deficient status were described. Marked increases in plasma and red cell folate levels were found in patients receiving folic acid supplements [284]. Folate pools are believed to contain enough quantity to satisfy folate requirements for at least 1 year in normal subjects [152]. Thus it may be necessary to retest MHD patients at least several months, if not more than 1 year, after the interruption of supplementation, to assess the risk of folate depletion. Moreover, most of these studies were conducted before the advent of high-flux/high-efficiency HD that appears to have dramatically increased the risk of folate deficiency in MHD patients. Livant et al. [282] found that of 32 MHD patients treated with high-flux polysulfone dialyzers, 5 individuals had reduced predialysis plasma folate concentrations and 4 had decreased red cell folate levels. The prevalence of folate deficiency might have been greater if 20 of the patients had not been prescribed folate supplements. Leblanc et al. [285] reported the folic acid clearance to be 134.7 ± 22.2 mL/min with high-flux/high-efficiency MHD, with a 26.3% decrease in plasma folate during an individual HD treatment. But whether there is a higher risk of folate depletion with high-flux membranes can be considered controversial, and folate status is not altered when using convective techniques [286,287]. The prevalence of folate deficiency in CPD patients is also controversial [32,158,288,289]. Folate losses into peritoneal dialysate averaged 107 μg/day in one study [32].

The influence of ESA therapy on folate status is reported later. Also, according to Biruete et al. [94], sevelamer binds folic acid, and this could impair its intestinal absorption. Soohoo et al. [290] reported that in 9517 incident MHD patients, after adjustment for case-mix, mortality was increased by 18% when serum folates were below 6.2 ng/mL. However, this relationship disappeared after adjustment for nutritional and inflammatory parameters. Folate nutriture in renal transplant patients is reported to be normal or decreased. The methylenetetrahydrofolate reductase (MTHFR) genotypes, labeled 677 and 1298, were shown to significantly influence plasma folate levels in 733 renal transplant recipients; the 677TT/1298AA group had lower plasma folate levels [291]. In a study concerning the incidence of telomere shortening in chronic dialysis patients and kidney transplant recipients who were followed for 1 year [292], the kidney transplant patients, who had undergone immunosuppression with AZA, had a significantly lower Hcy levels, and similar serum folate levels and telomere length as compared to the chronic dialysis patients. On the other hand, those kidney transplant patients who were treated with mycophenolate mofetil, in comparison to patients who received AZA, presented after 1 year with similar plasma Hcy levels, increased serum folate concentrations and telomere shortening. These findings highlight the complexity of the relationships between these factors [292].

In 75 AKI patients undergoing CRRT, folic acid was found deficient 33% of the patients [160]. In 10 patients receiving treatment with CVVH or hemodiafiltration, the amount of folic acid removed was estimated to be 650 nmol/day, with the folate clearance equal to about 76% of the urea clearance [203]. In 40 patients treated with CVVHD, Datzmann et al. [35] found constant daily losses of folic acid and vitamin B12 during the life of the filter (72 hours). The losses were compensated by the daily supplements of the vitamins.

Clinical consequences of folate nutriture in advanced chronic kidney disease

Folate and anemia

The advent of the EPO era for chronic dialysis patients increased interest in the body pools and nutritional requirements for vitamins that were directly involved in erythropoiesis, such as vitamin B12 and folates, as well as for iron. There has been concern that in patients beginning EPO treatments, the nutritional needs for these vitamins would increase because of increased utilization during intensive erythropoiesis, and that inadequate body pools of these vitamins (or iron) would reduce the effectiveness of EPO. Mydlik et al. [219] reported a significant decrease of erythrocyte folic acid after 1 year of EPO therapy in 15 MHD patients, suggesting increased utilization with ESA therapy. This was not confirmed by Pollock et al. [293] who did not find differences in folate and vitamin B12 concentrations before versus after 18 months of EPO treatment in 81 MHD and 31 CPD patients. No information was given as to whether the patients in these last two studies received folic acid or vitamin B12 supplements. In a metaanalysis of the treatment of ESA resistance in chronic dialysis patients, only two studies met the selection criteria for analysis, and no evidence emerged to support vitamin supplementation for patients with ESA resistance [294]. In the KDIGO guidelines on anemia management, no vitamin adjuvants, such as folates, vitamin B12, or vitamin C, are recommended with ESA therapy [268]. The KDOQI guideline on nutrition in CKD does not provide recommendations on this matter [1].

Folic acid, Hcy, and methylenetetrahydrofolate reductase gene polymorphisms

Increased plasma Hcy is a recognized CV risk factor in the general population, and elevation of plasma Hcy in advanced CKD and chronic dialysis patients has been recognized for at least two decades. Hcy-mediated tissue damage has been extensively reviewed [295] and includes increased oxidant stress, impairment of nitric oxide synthesis at the endothelial level, proliferation of smooth muscle cells, and activation of inflammation, all of which participate in the genesis of atherosclerosis. The possibility that reducing plasma Hcy might improve outcomes in advanced CKD, chronic dialysis, and kidney transplant patients has been tantalizing. Hcy is an intermediate compound in the formation of cystathionine from methionine (Fig. 26.6). Three vitamins, B6, B12, and folates, are directly involved in its synthesis and metabolism. The formation of cysteine from methionine requires vitamin B6. PLP is a coenzyme for cystathionine synthase, which transforms methionine to cystathionine, and for cystathionase, which cleaves cystathionine to form cysteine. Vitamin B12 and folate participate in the remethylation of Hcy leading to the reformation of methionine. As suggested in Fig. 26.6, PLP or folate deficiency, which occurs not infrequently in CKD and chronic dialysis patients, could contribute to the rise in plasma Hcy in CKD and chronic dialysis patients. However, CKD patients who have normal levels of folate, cobalamin, and PLP still manifest increased plasma Hcy [296]. In advanced CKD and chronic dialysis patients, plasma Hcy concentrations tend to be about one and one-half to two times the values in healthy controls and correlate inversely with the GFR [297,298]. However, plasma Hcy levels are influenced by the nutritional status and may be low in MHD and CPD patients who have protein–energy wasting (PEW) [299]. Plasma Hcy is also increased in nondialyzed children with advanced CKD and in children undergoing MHD. Arnadottir et al. [300] found that 6 months after renal transplantation, plasma Hcy concentrations had decreased by an average of 14% but were still significantly higher in the renal transplant recipients as compared to a control group matched for renal function.

Plasma Hcy is affected by the dialysis technique. Despite a greater intradialytic decrease in plasma Hcy with high versus low-flux membranes (42% vs 32%), no difference was found in predialysis plasma Hcy levels in patients treated for 3 months with high- as compared to low-flux dialyzer membranes [301]. Pedrini et al. [302] found in a randomized crossover trial that online hemodiafiltration sustainably decreases predialysis Hcy levels when compared to low-flux conventional HD. Vychytil et al. [303] studied peritoneal losses of Hcy in 39 CPD patients. Daily peritoneal Hcy removal (38.9 ± 20.8 μmol/day) was correlated with plasma Hcy, effluent volume, and the D/P creatinine ratio [304]. Free Hcy represented 47.5% and 75.2% of total Hcy in plasma and dialysate, respectively. It was concluded that CPD, like MHD, is not sufficiently effective to normalize plasma Hcy levels.

A number of years ago, two prospective studies described the association between plasma Hcy and CV risk in CKD patients and found elevated plasma Hcy to be a risk factor for endothelial dysfunction and CV disease in CKD patients [305]. Moustapha et al. [306] followed 167 ESRD patients for a 17.4-month period and reported an increased CV morbidity and mortality risk of 1% for each μmole rise in plasma Hcy. In CPD and MHD patients, Bostom et al. [307] found a relative risk for nonfatal and fatal CV events of 3.0 and 4.4, respectively, when comparing the highest quartile versus the lower three quartiles of plasma Hcy levels during a follow-up of 17.0 months. However, Kalantar-Zadeh et al. [308] found an increased mortality in the lowest quartile of plasma Hcy in 367 MHD patients, even after adjustment for their nutritional and inflammatory states. These authors concluded that Hcy is an independent nutritional marker, and this explained the negative association between plasma values and patient outcomes. The role of Hcy regarding patency of the vascular access is also controversial. Whereas Shemin et al. [309] found a significant relationship between high plasma Hcy levels and vascular access thrombosis in an 18-month prospective study involving 84 HD patients, Bowden et al. [310] found no difference in plasma Hcy levels between 52 MHD patients with more than one episode of vascular access thrombosis and 133 MHD patient controls who did not have vascular access thrombosis during a 16-month prospective study. In a prospective study of 733 renal transplant recipients, Winkelmayer et al. [311] found that the risks of graft loss and patient death were each associated with plasma Hcy levels >12 μmol/L with hazard ratios after the adjustment of 1.63 and 2.44, respectively.

Many studies have examined the effect of lowering plasma Hcy levels with vitamin therapy in nondialyzed advanced CKD patients, in chronic dialysis patients, and in renal transplant recipients. The findings can be summarized as follows. The usual effect of folic acid therapy is a 30%−50% decrease in plasma Hcy, but with few patients attaining normal plasma Hcy levels. The magnitude of the Hcy-lowering effect of folic acid is positively related to the pretreatment plasma Hcy values and is negatively associated with the baseline RBC folate concentrations. Most clinical trials in advanced CKD and chronic dialysis patients that used low doses (2.5−5 mg/d) of folic acid to reduce plasma Hcy levels show about the same magnitude of Hcy reduction as in the trials that used larger folic acid doses. Bostom et al. [312] reported a more effective plasma Hcy-lowering effect of a combination of folic acid, vitamin B6, and vitamin B12 in renal transplant recipients than in MHD patients.

Subsequent large-scale, prospective trials addressed the effectiveness of Hcy-lowering therapy on clinical outcomes in CKD patients. The HOST trial included 2056 nondialyzed advanced CKD patients and chronic dialysis patients who were randomized in a double-blind fashion to receive each day either a combination of three vitamins, folic acid, 40 mg; pyridoxine hydrochloride (vitamin B6), 100 mg; and cyanocobalamin (vitamin B12) 2 mg, or placebo [298]. The average duration of follow-up was 3.2 years. Although plasma Hcy fell significantly in the treated group, this group experienced no greater decrease in overall mortality or CV events. In a substudy of this trial, cognition was analyzed as an outcome and also was not improved by the Hcy-lowering therapy [313]. Heinz et al. [314] enrolled 650 MHD patients in a randomized controlled trial that also compared a combination of folic acid, vitamins B6, and B12 to placebo. Again, no difference was found in clinical outcomes (overall and CV mortality and CV events). In a large randomized double-blind prospective trial of 4058 renal transplant patients, the Folic Acid for Vascular Outcome Reduction in Transplantation trial examined the effects of a high daily dose of vitamin supplements (folic acid 5 mg, cyanocobalamin 1 mg, and vitamin B6 50 mg) compared to a lower daily dose of vitamins (no folic acid, vitamin B6, 1.4 mg and cyanocobalamin, 2 μg) [315]. No difference was found between the two groups with regard to the composite primary endpoint (CV death and CV events). In the Diabetic Intervention with Vitamins to Improve Nephropathy (DIVINe) study, in which 238 nondialyzed diabetic CKD patients were randomized to receive vitamin B12 (1 mg/d), B6 (25 mg/d), and folic acid (2.5 mg/d) supplements or placebo, CKD progression was faster, and the CV events were more frequent in the group receiving the vitamin therapy even though they experienced a significant decrease in plasma Hcy [316]. Metaanalyses that include either nondialysis-dependent CKD or ESKD or with a functioning kidney transplant [317] or only MHD and/or CPD patients [318] have concluded that the use of vitamin supplements that lower plasma Hcy does not reduce overall or CV mortality.

MTHFR gene polymorphism plays an important role in Hcy and folic acid metabolism and also in the Hcy response to vitamin B supplements [319]. The main variants are at positions 677 (MTHFR 677C > T), 1298 (MTHFR 1298A > C), 1317 (MTHFR 1317T > C), and 1793 (MTHFR 1793G > A). Trovato et al. [320] found in 630 Italian MHD patients a lower frequency of MTHFR 677C > T and MTHFR 1298A > C than in controls who did not have significant renal disease, suggesting that a relationship between this polymorphism may protect against kidney damage. Also, Achour et al. [321] reported that the response of plasma Hcy levels to folic acid and vitamin B12 supplements was related to the presence of the MTHFR 677 phenotype. In a subgroup of 1671 CKD stage 3 hypertensive patients from the China Stroke Primary Prevention Trial (CSPPT), enalapril, 10 mg/d, and folic acid, 0.8 mg/d, reduced CKD progression by 56% and the number of patients with a rapid rate of eGFR decline (> 5 mL/min/1.73 m^2/year) by 44% when compared to CKD stage 3 patients receiving enalapril, 10 mg/d, alone. Diabetic CKD 3 patients and MTHFR C677 CC and CT phenotypes demonstrated the greatest degree of slowing of eGFR loss with folate therapy, whereas the decrease in plasma Hcy was greater in the MTHFR C677 TT phenotype. Capelli et al. [295] explained the discrepancies in outcomes among the CSPPT, DIVINe, and the HOST studies on CKD progression by pointing out that the daily folate dose was much different and much lower in the CSPPT study (0.8 mg) than in the DIVINe and HOST studies (2.5 and 40 mg, respectively). Also, there is no folic acid fortification of foods in China, in contrast to the United States (HOST study) and Canada (DIVINe study). So, the usual daily intake of folate is probably substantially less in the Chinese population as compared to the US and Canadian populations.

It is emphasized that the controversy regarding vitamin supplements to lower plasma Hcy in CKD, chronic dialysis, and kidney transplant patients is related to the rather mild increase in plasma Hcy that occurs due to the reduced GFR. Patients with inborn errors of metabolism that cause severe, dangerous hyperhomocysteinemia who have plasma Hcy concentrations that are far greater than 1.5–2.0 times the normal levels that are usually observed in CKD should be given vitamin therapy to lower their plasma Hcy concentrations.

Folate supplementation in advanced chronic kidney disease, chronic dialysis, and kidney transplant patients

Folic acid supplements appear to be safe for advanced CKD, chronic dialysis, and kidney transplant patients, even at the range of doses prescribed to reduce plasma Hcy levels. An acute, large load of folic acid may cause AKI in rodents, but this has not been observed in humans [322]. There is the possibility that folate treatment would resolve the hematological disturbances caused by vitamin B12 deficiency, without improving the neurological disorders, or that metabolites of folate might be toxic, possibly by inhibiting the cellular transport of folate. Possible mild side effects of folate, such as nausea, headache, or vivid dreams, have been reported, usually with doses of 5 mg/d or greater [323]. Although many of the more recent studies indicate that plasma and red cell folate levels are usually normal in CKD and chronic dialysis patients, some patients still have low folate concentrations, and high-efficiency/high-flux dialysis may increase the risk of folate deficiency; but this is controversial [282,285]. A low-protein diet usually provides a daily folic acid intake below the RDA. Also, as indicated earlier, there may be endogenous as well as exogenous (i.e., medicinal, Table 26.2) inhibitors of folate in renal failure, and this inhibition might not be reflected in the plasma or red cell folate levels. Moreover, dietary intake of folates may vary substantially, since these patients are often fragile and develop intercurrent illnesses, and body folate pools may be rather quickly depleted. Hence, we recommend a daily folic acid supplement in the order of the RDA (400 μg) up to 1 mg of folic acid for CKD 3–5, MHD, and CPD patients (Table 26.4). This recommendation differs from the current KDOQI nutrition update in which routine folic acid supplementation of CKD 3–5D patients is not recommended [1]. No folic acid supplement is suggested for the treatment of the modestly increased plasma Hcy levels that commonly occur in chronic kidney failure. This elevation of plasma Hcy has not been shown to have adverse effects; see the earlier discussion on plasma Hcy in CKD.

Summary:

- Folate metabolism is abnormal in advanced CKD.
- Dietary folate intake is frequently below the RDA in nondialyzed advanced CKD, MHD, CPD, and kidney transplant patients and chronic dialysis.
- Serum folate levels are often but not always reported to be low in MHD and CPD patients.
- The common prescription of potassium-restricted diets probably contributes to the low folate intake in at least the first three of these patient groups.
- AKI patients receiving CRRT often have low serum folate levels.
- Whether there is a high prevalence of folate deficiency in advanced CKD patients is not clearly established, in

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part, because functional studies to assess for folate deficiency are lacking.
- Whether convective hemodialysis techniques can induce folate deficiency remains controversial.
- Routine folic acid supplementation is not currently recommended for the anemia management of advanced CKD patients receiving erythropoiesis stimulating agents.
- Increased plasma Hcy is very common in advanced CKD and chronic dialysis patients and is associated with adverse clinical outcomes in some but not all studies.
- Folic acid supplements or the combination of folic acid, vitamin B6, and vitamin B12 supplements reduce elevated plasma Hcy to near-normal or normal levels.
- The combination of folic acid, vitamin B6, and vitamin B12 supplements do not improve clinical outcomes in advanced CKD, chronic dialysis, and kidney transplant patients.
- A low dose of folic acid (0.8 mg/d) in combination with the angiotensin converting enzyme inhibitor lisinopril, 10 mg/d, was observed to reduce the rate of GFR decline in nondialyzed Chinese CKD patients.
- Although the KDOQI guidelines on nutrition in CKD do not recommend routine administration of folic acid, we recommend a folic acid supplement of 0.4–1.0 mg/d should be routinely prescribed to advanced CKD, MHD, CPD, and kidney transplant patients and to AKI patients receiving renal replacement therapy.

Vitamin B12, physiology, biochemistry, and nutritional status in chronic kidney disease patients

Vitamin B12 physiology and biochemistry

Vitamin B12 (cobalamin, Table 26.1) is the "extrinsic factor" (i.e., present in food) which, when combined with the "intrinsic factor" (present in gastric juice), results in the absorption of the antipernicious anemia factor which came to be identified as vitamin B12. The vitamin B12 structure consists of a corrin nucleus, a nucleotide, and a cobalt atom. Cobalamins are unstable in light and destroyed by strong oxidation and reduction agents. Cyanocobalamin, the pharmaceutical form of vitamin B12, has been isolated from liver extracts. Coenzyme B12 and methylcobalamin are the metabolically active forms of vitamin B12. All forms of B12 in large doses are equally effective [324]. The only natural source of vitamin B12 is bacterial synthesis. Cobalamins are present in animal tissues, mostly liver, meat and seafood, and in lesser amounts in egg yolk and milk. Very small amounts are present in fruits and vegetables. Physiological intestinal absorption follows several steps: free cobalamin is combined with a salivary peptide binder which then is released in the small intestine by trypsin where it then combines with the intrinsic factor, a glycoprotein molecule of gastric origin. Absorption of the vitamin B12-intrinsic factor complex occurs after binding to a receptor on the brush border of mucosal cells in the ileum. Large pharmacological doses of cobalamins may be absorbed by the small intestine via passive diffusion. Three binding proteins (transcobalamins I, II, and III) participate in cobalamin transport in plasma and in the in vivo storage of vitamin B12. Cobalamin stores can constitute up to several milligrams of vitamin B12 and may prevent vitamin B12 deficiency from occurring for several years after intestinal absorption ceases [152] (Table 26.1). Vitamin B12 is not catabolized and is excreted in bile, with an efficient enterohepatic cycle. Vitamin B12 assessment was formerly performed by microbiologic assays and, more currently, by radioimmunoassay. Vitamin B12 plays a key role in folate metabolism and participates in the demethylation of methyltetrahydrofolate (MTHF) and methylation of Hcy (Fig. 26.6). This step is essential for the regeneration of THF, which is involved in DNA synthesis by thymidylate synthesis, and for folate delivery to tissues. In the absence of demethylation of MTHF, signs of folate deficiency may occur [324]. Furthermore, vitamin B12 is required for myelin synthesis, as demonstrated by the severe neurological disturbances that may occur with pernicious anemia. The exact mechanism of cobalamin action on myelin is unknown. Several medications may interfere with vitamin B12 metabolism or actions. They are summarized in Table 26.3.

Vitamin B12 intake in chronic kidney disease

In the general population with normal GFR, the upper quintile of vitamin B12 intake has been associated with a lower incidence of CKD [14]. The amount of vitamin B12 in diets comprising 40 or 60 g of protein per day is clearly below the RDA (Table 26.2 from Stein et al. [15]). A study from Poland indicates that vitamin B12 intake is below the EAR in almost 50% of nondialyzed advanced CKD and kidney transplant patients, and in 60% of MHD and CPD patients who were not receiving vitamin supplements [4]. Martin-Del-Campo et al. [18] reported that a slightly lower proportion of CPD patients, 40%, had a vitamin B12 intake below the DRI. However, in an earlier study, Wang et al. [17] reported an adequate vitamin B12 intake in most CPD patients.

Nutritional vitamin B12 status in advanced chronic kidney disease and chronic dialysis patients

Plasma vitamin B12 is usually within the normal range in advanced CKD patients. In a study by McMahon et al.

[325] from the Framingham and NHANES cohorts, plasma vitamin B12 was not associated with albuminuria or kidney function. However, higher plasma vitamin B12 levels were associated with reduced kidney function in the presence of high plasma Hcy levels in both cohorts. This was attributed to a possible resistance to the effect of vitamin B12 on plasma Hcy metabolism [325]. Notwithstanding the frequent occurrence of low intakes of vitamin B12 in advanced CKD and chronic dialysis patients (see previous section), serum values of B12 tend to be normal in these individuals (see next section). In MHD patients, even without B12 supplementation and even with years of MHD treatment, serum vitamin B12 is almost always in the normal range [157]. Fehrman-Ekholm et al. [287] did not find decreased serum vitamin B12 levels in hemodiafiltration patients. The normal serum vitamin B12 levels in most advanced CKD and chronic dialysis patients may be due to their inability to excrete vitamin B12 in the urine. In addition, because cobalamin is a large molecule (MW, 1355) and is protein-bound, losses of vitamin B12 into dialysate are low. In CPD patients, no cobalamin was recovered in peritoneal fluid by Boeschoten et al. [32]. Intriguingly, Soohoo et al. [290] reported a higher mortality in patients who were in the three highest quintiles of serum vitamin B12 levels among a cohort of 12,968 incident MHD patients, even after adjustment for comorbidities and nutritional status. This finding has been interpreted as possibly due to a transcobalamin imbalance with increased transcobalamin 1 and 3 maintaining a high plasma vitamin B12 level and decreased transcobalamin 2, which is lower due to inflammation, reducing tissue uptake of vitamin B12.

An inborn error engendering cobalamin deficiency has been described. Cobalamin C deficiency may be caused by mutations of the MMACHC gene (methylmalonic aciduria cblC type with homocystinuria). These mutations lead to a deficit of two active coenzyme derivatives of cobalamin, adenosylcobalamin, and methylcobalamin. This may be responsible for some cases of atypical HUS in children and in young adults [326]. In addition to the microangiopathic lesions found with HUS, typical histological findings include a vacuolated appearance of the glomerular basement membrane and IgM staining of the glomerular capillary wall. This syndrome is dramatically improved by the correction of the cblC defect with parenteral injections of hydroxocobalamin, and, therefore, it is important to consider cblC deficiency in the diagnostic evaluation of atypical-HUS, even when it occurs in adults.

Vitamin B12 and anemia management in chronic kidney disease

Please refer to the same paragraph in the section on folate.

Vitamin B12 and Hcy

Please refer to the Hcy discussion in the section on folate.

Vitamin B12 supplementation in advanced chronic kidney disease, chronic dialysis, kidney transplant, and acute kidney injury patients

Vitamin B12 deficiency is unusual in CKD and chronic dialysis patients, and most authors do not think that vitamin B12 supplements are necessary (Table 26.4). The KDOQI guidelines also do not recommend routine supplements of vitamin B12 [1]. On the other hand, a daily supplement of 2.4 μg of vitamin B12, which is the RDA, is safe and inexpensive and might occasionally help to prevent vitamin B12 deficiency. A vitamin B12 supplement is recommended for AKI-3 patients who are receiving renal replacement therapy (see Chapter 35: Metabolic Management and Nutritional Support in Acute Kidney Injury).

Summary:

- Advanced CKD and chronic dialysis patients are usually reported to have normal serum vitamin B12 levels without clinical manifestations of vitamin B12 deficiency, even though studies describe low dietary vitamin B12 intakes in these patients.
- Losses of vitamin B12 during the dialysis procedure are very low because of the relatively large size of cyanocobalamin and the binding of this vitamin to plasma proteins.
- One observational study has reported increased mortality in MHD patients who have high serum vitamin B12 levels; this finding remains to be confirmed.
- Cobalamin C deficiency due to mutation of the MMACHC gene can cause AKI from thrombotic microangiography.
- A routine supplement of 2.4 μg of vitamin B12 per day, which is the RDA, is recommended for CKD 1−5D patients and kidney transplant recipients, and for AKI patients receiving renal replacement therapy.

Niacin (vitamin B3) physiology, biochemistry, and nutritional status in chronic kidney disease patients

Niacin physiology and biochemistry

Niacin is the therapeutic agent for pellagra, a condition described initially in maize-eating populations [327]. Niacin is a generic term, including nicotinic acid and nicotinamide (Table 26.1). Active coenzymes from niacin are the pyridine nucleotides, nicotinamide adenine dinucleotide (NAD), and NAD phosphate (NADP). High amounts of NAD and NADP (the main forms of niacin intake from foods) are present in meat, fish, legumes, coffee, and tea. These compounds are hydrolyzed in the intestine to yield nicotinamide and then nicotinic acid. However, niacin bioavailability may be reduced because of its binding to carbohydrate and peptide macromolecules. Intestinal absorption by passive diffusion is efficient, even for large doses of niacin. Tryptophan is a precursor of niacin, and tryptophan intake alone may be sufficient to provide the RDA (recommended dietary allowance) for nicotinic acid. Niacin is quickly removed from plasma by tissues (mainly by liver and erythrocytes) where it is converted to coenzyme forms. Storage, mostly in the liver, is limited, and signs of pellagra may occur within 50–60 days in humans fed a corn diet deficient in niacin. Excess niacin is methylated in the liver, and the methylated metabolites are excreted in the urine. Niacin status is assessed by measuring nicotinic acid and nicotinamide in blood and red cells, formerly using microbiological assays and currently by chemical measurements or HPLC. The NAD/NADP ratio in red cells, which is decreased in niacin deficiency, may be used as an indicator of niacin depletion in kidney failure patients.

Pyridine nucleotides are involved in at least 200 enzymatic reactions. These may include NAD that is mainly involved in catabolic reactions, such as oxidation of energy substrates, and NADP that is primarily concerned with biosynthetic processes, such as for steroids. These coenzymes are key elements for carbohydrate, fatty acid, and amino acid metabolism. There is a close relationship between the metabolism of niacin and other vitamins. Vitamin B6 and riboflavin are necessary for niacin synthesis from tryptophan. Niacin is necessary for the synthesis of active forms of vitamin B6, riboflavin, and folic acid. Pharmacological doses of nicotinic acid reduce serum total cholesterol, increase the HDL-cholesterol fraction, and decrease serum LDL and VLDL fractions and triglycerides [328]. The mechanisms involved in these different effects on lipids appear to be complex and differ from one fraction to another [329,330]. Dermal flush and skin-related symptoms with niacin therapy have been characterized by the NASTy acronym (niacin-associated skin toxicity) and are an important limitation to treatment with niacin [329]. They relate to the stimulation of G protein–coupled receptor 109A which is distributed widely on immune cells and especially in skin cells. The stimulation of this receptor by an agonist triggers NASTy but does not reproduce the lipid effects of niacin as shown by Olson et al. [330]. Another important property of nicotinamide is the inhibition of the Na/Pi type IIb cotransporter (NaPi-2b) and the type IIa cotransporter (NaPi-2a) in the intestinal brush border and in the proximal renal tubular epithelial cells of the kidneys, respectively [331]. Large, pharmacological doses of nicotinamide, 500–1500 mg/d given twice daily, by inhibiting active intestinal phosphate transport, can reduce serum phosphorus concentrations in advanced CKD and chronic dialysis patients. Several medicines may interfere with niacin metabolism or actions. They are summarized in Table 26.2.

Dietary niacin intake in chronic kidney disease

Data regarding niacin intake in CKD are conflictory. Low-protein diets containing 40- to 60-g protein per day may not provide the RDA for niacin (Table 26.3; [15]). However, in 210 stages 4–5 CKD patients, only 1% were reported to have a niacin intake below the recommendation of the National Health and Medical Research Council Nutrient Reference Values for the general Australian population [16]. This contrasts with the findings of Jankowska et al. [4] that about 30% of nondialyzed CKD, chronic dialysis, and kidney transplant patients were deficient in their niacin intake. In this latter study, about 40% of MHD and CPD patients displayed a niacin intake below the EAR. Martin-Del-Campo et al. [18] reported that two-thirds of CPD patients had niacin intakes below the DRI. Bossola et al. [3] found from 3-day diet diaries that the niacin intake was below the RDI in 86% of 128 MHD Italian patients.

Nutritional niacin status in advanced chronic kidney disease, chronic dialysis, and kidney transplant patients

Because of its rapid metabolic clearance from plasma, losses of niacin in dialysate would be expected to be low. Ramirez et al. [148] did not find differences between pre- and postdialysis red cell niacin concentrations in MHD patients. No data are available concerning niacin losses into peritoneal dialysate. DeBari found in MHD patients low niacin concentrations in leukocytes, but normal niacin content in red cells [332]. Ramirez et al. [148,194] did not find low niacin levels in whole blood or erythrocytes of MHD patients who were not receiving vitamin supplements or in whom such supplements had been stopped for at least 1 year.

Clinical syndromes involving niacin in acute kidney injury and chronic kidney disease patients

Depletion of NAD is a proposed risk factor for AKI in postoperative patients. This raises the possibility that nicotinamide supplements might be used to prevent AKI in these individuals [333]. In CKD, pellagra (characterized by diarrhea, dementia, and dermatitis) has never been reported, but niacin deficiency has been suggested as the cause of onycholysis in MHD patients [334]. A post hoc analysis was conducted involving 509 stage 3 CKD patients from the Atherothrombosis Intervention in metabolic syndrome with low HDL/HIGH Triglycerides trial (AIM-HIGH trial) [335]. This trial failed to demonstrate a benefit to adding extended-release niacin to simvastatin with regard to the incidence of adverse CV events. The post hoc analysis indicated that in people with stage 3 CKD, niacin therapy significantly increased serum HDL and reduced serum triglycerides without an effect on CV events but with an increase in the overall mortality (hazard ratio, 1.73). It is not known why overall mortality increased in the people with stage 3 CKD who were given niacin. The trial used a pharmacological dose of extended-release niacin [1500–2000 mg/d that is at around 100 times the RDA (14–16 mg/d, Table 26.4)].

Large doses of niacin have been proposed to treat hyperphosphatemia in CKD, because of the capacity of niacin to inhibit the Na–Pi cotransporter in the intestinal tract [336]. The usual side effects of the molecule, hepatotoxicity, and flush were reduced by changing the formulation from immediate to extended-release and were also less pronounced with niacinamide then with nicotinic acid. A decrease in platelets was encountered with both forms of niacin, nicotinic acid, and nicotinamide, but this is observed inconsistently. The potential advantages of niacin as a phosphate absorption inhibitor are the low cost, the absence of calcium or other cations that are often found in intestinal phosphate binders, the potential benefits on the lipid profile, a potentially lower pill burden, and the fact that the medicine can be taken at a time that is independent of meals [331]. Another post hoc analysis of the AIM-HIGH trial evaluated the effect of niacin therapy on serum phosphate concentrations and other mineral markers in 352 patients with an eGFR less than 60 mL/min/1.73 m^2. After 3 years of treatment, serum phosphorus had decreased by 0.25 mg/dL in the extended-release niacin group, but no difference was observed regarding serum PTH, FGF-23, calcium, or vitamin D [337]. The effectiveness of nicotinamide as a Pi binder was compared to sevelamer in the NICOREN study [338]. In this open label, randomized study involving 100 MHD patients, serum phosphorus levels were similar after 24 weeks of treatment in the two groups. However, nicotinamide did not reach the significant noninferiority criterion because the number of participating patients was lower than planned and because there was a higher treatment discontinuation rate (60% higher in the nicotinamide group than in the sevelamer group). Also, four patients who were assigned to nicotinamide treatment developed a low platelet count; none who received sevelamer experienced this adverse event. In a recent metaanalysis involving nine studies and 428 MHD patients, serum phosphorus, PTH, and the CaxPi product were lower in the niacin-treated patients as compared to placebo, and the increased risk of thrombocytopenia with niacin was confirmed [339]. The thrombocytopenia with niacin treatment was mild, and no serious adverse events were reported. Thus clinical trials confirm that niacin effectively decreases serum phosphorus in nondialyzed advanced CKD and chronic dialysis patients. However, the effects of niacin treatment on morbidity, mortality, and quality of life outcomes are still lacking.

Niacin supplementation in chronic kidney disease, chronic dialysis, kidney transplant, and acute kidney injury patients

A low-protein diet may provide only small amounts of niacin, and some studies have demonstrated a niacin intake below the RDA or DRI in chronic dialysis patients [3,4,18]. We, therefore, recommend the RDA of niacin, 14–16 mg/d, as a supplement for CKD 3–5, chronic dialysis, and kidney transplant patients. AKI patients receiving renal replacement therapy should also receive 14–16 mg/d of niacin. The use of niacin as phosphate-lowering or as a cholesterol-lowering therapy in CKD 3–5, including chronic dialysis patients, is discussed earlier. No specific recommendation has been made for niacin supplementation in the KDOQI nutrition guidelines other than to encourage CKD 1–5D and CKD T1–5 patients to ingest diets providing sufficient amounts of all vitamins and to consider multivitamin supplements for individuals with inadequate vitamin intakes [1] (Table 26.4).

Summary:

- In advanced CKD and chronic dialysis patients, niacin intake is often reported to be below the RDA, but blood and red cell levels of niacin generally are normal.
- Clinical syndromes of niacin deficiency (e.g., pellagra) have not been reported in advanced CKD and chronic dialysis patients.
- Niacin can effectively inhibit intestinal phosphate absorption and reduce serum phosphorus levels but may cause flushing, gastrointestinal symptoms, hepatotoxicity, hyperuricemia, and thrombocytopenia.
- More research is needed concerning the effects of niacin on serum lipids (an increase in serum HDL, a lowering of serum triglycerides) in advanced CKD, chronic dialysis, and kidney transplant patients.

Continued

- In stage 3 CKD patients in the AIM-HIGH trial, adding a pharmacological dose of niacin (1500–2000 mg/d) to simvastatin did not change CV outcomes and was associated with increased overall mortality.
- Although niacin deficiency appears to be uncommon in advanced CKD and chronic dialysis patients, since the dietary niacin intake is often below the RDA, a routine supplement of 14–16 mg of niacin per day, which is the RDA, is recommended for CKD 1–5D patients and kidney transplant recipients, and for AKI patients receiving renal replacement therapy.

Biotin (vitamin B8) physiology, biochemistry, and nutritional status in chronic kidney disease patients

Biotin physiology and biochemistry

Biotin (vitamin B8) is a bicyclic compound containing an ureido ring and a tetrahydrothiophene ring (Table 26.1). Although biotin is synthetized by intestinal flora, whether this synthesis is sufficient to satisfy the daily need for biotin in humans is controversial [340]. The main food sources of biotin are liver, egg yolk, soybean, and yeast. Cereals, legumes, and nuts contain moderate amounts of biotin, and fruits and vegetables are poor sources of biotin, except for cauliflower and mushrooms. Biotin absorption occurs mainly in the jejunum and requires the release of biocytin (biotinyl-lysine) from ingested proteins and the action of biotinidase to separate lysine and biotin, which are each absorbed by a diffusive saturable process. Long-term treatment with anticonvulsant medicines, such as carbamazepine and primidone, may interfere with biotin absorption at the intestinal brush border [341]. Other medications may interfere with biotin metabolism or actions (see Table 26.2). Avidin, a glycoprotein that strongly binds to biotin, may also impair intestinal biotin absorption. Free biotin and its metabolites are excreted in the urine. Biotin stores appear to cover biotin needs for about 1 month. A biotin-deficient diet in human volunteers can lead to symptoms of deficiency in 5 weeks [342]. Formerly assessed by microbiological assays, today plasma biotin is commonly measured by ultrahigh performance liquid chromatography–tandem mass spectrometry [343]. Biotin mainly acts as a "CO_2 carrier" being the coenzyme for 5-carboxylases (acetyl-CoA carboxylase, pyruvate carboxylase, propionyl-CoA carboxylase, and B methylcrotonyl-CoA carboxylase). Biotin is covalently bound to the ε-amino group of a lysine residue of carboxylases. Thus it plays an important role in the metabolism of carbohydrates, fatty acids, and some amino acids. Experimental biotin deficiency was induced in seven healthy human volunteers who were given a biotin-free diet and an excessive intake of raw egg white (rich in avidin). In 5 weeks the subjects developed mild depression, somnolence, muscle pain, hyperesthesia, anorexia, and later a maculosquamous dermatitis with a greyish pallor and fine desquamation. All symptoms disappeared within 5 days of starting biotin injections [340]. Alopecia is also a common feature of biotin deficiency [342].

Dietary biotin intake in chronic kidney disease

Biotin intake is often below the RDA when daily protein intake is 80 g or less per day (Table 26.3) [15]. However, no data regarding biotin intake in nondialyzed advanced CKD, chronic dialysis, and kidney transplant patients are currently available.

Nutritional biotin status in advanced chronic kidney disease and chronic dialysis patients

Uremic toxins have been shown to impair tubulin polymerization which, under normal conditions, leads to cellular microtubule formation. Biotin counteracts the effects of uremic toxins on tubulin [344]. Several studies did not find biotin deficiency in advanced CKD patients. Biotin concentrations in plasma, leukocytes, and RBC were found to be high in MHD patients [345] and even higher in anuric MHD patients and in long-term MHD patients [152]. Other studies have confirmed high plasma biotin levels in MHD patients [346]. In this last study, 16 MHD patients complaining of skeletal muscle cramps had higher plasma levels of biotin and biotin metabolites than MHD patients without cramps. However, biotin supplementation (1 mg/d) relieved cramps in seven of these patients [346]. Very high biotin plasma levels were reported in one MHD and one CPD patient who received biotin supplements (5 mg/d, and an unknown amount, respectively) [347]. Their plasma biotin levels were 82 nmol/L (normal values, 0.8–3.2 nmol/L). These exceptionally high values have caused erroneous and contradictory measurements for serum thyroid stimulating hormone (TSH), thyroxin (T4), and PTH, which were explained by competition between the high biotin plasma levels and the biotinylated antibodies used in the hormone assays.

Biotin supplementation in chronic kidney disease, chronic dialysis, and kidney transplant patients

There is no Institute of Medicine RDA for biotin intake for healthy subjects, but there is an estimation of the dietary biotin need which is referred to as the AI [348]. In the absence of sufficient data to estimate the RDA, the AI is often proposed. The AI is a value based on the average nutrient intakes or experimentally derived intakes in a group of apparently healthy people who are expected to meet or exceed the amount needed to maintain a state of adequate nutrition in essentially all members of that group. The AI for healthy, normal men and healthy, normal nonlactating women is 30 μg/d (Table 26.4). Whether there is a need for supplemental biotin in CKD 3—5D, kidney transplant or AKI patients is unknown. Biotin deficiency is not reported in CKD 3—5D patients. However, the daily biotin intake with a low-protein diet is below the AI. Again, because CKD 3—5, MHD, and CPD patients not uncommonly have low intakes of many nutrients, it is recommended that they receive a daily biotin supplement equal to the AI, 30 μg/d, for normal men and nonlactating women (Table 26.4). There is no recommendation for biotin in the recent KDOQI nutrition guidelines other than to encourage CKD 1—5D and CKD T1—5 patients to ingest diets providing sufficient amounts of all vitamins and to consider vitamin supplements to prevent or treat micronutrient deficiencies in individuals with persistently inadequate vitamin intakes [1] (Table 26.4).

Summary:

- Plasma, RBC, and white cell biotin concentrations are usually reported to be normal in nondialyzed advanced CKD and chronic dialysis patients.
- No data are currently available regarding the dietary biotin intake of CKD or chronic dialysis patients.
- No specific diseases related to increased or decreased body biotin levels have been reported in nondialyzed advanced CKD patients or chronic dialysis patients.
- Biotin supplements can cause very high plasma biotin levels which may interfere with laboratory tests that use biotinylated antibodies; for example, for the measurement of TSH, T4, and PTH.
- The recommended daily intake for biotin for CKD and chronic dialysis patients is the AI for healthy normal men and healthy, normal nonlactating women, which is 30 μg/d.
- Because CKD 3—5, MHD, and CPD patients not uncommonly have low intakes, it is recommended that they routinely receive a daily biotin supplement equal to the AI, 30 μg/d.

Pantothenic acid (vitamin B5) physiology, biochemistry, and nutritional status in chronic kidney disease patients

Pantothenic acid physiology and biochemistry

Pantothenic acid or "chick antidermatitis factor" is formed from the combination of pantoic acid and β-alanine. Some of its characteristics are given in Table 26.1. Pantothenic acid is used in the formation of CoA and acyl carrier proteins (ACPs), which carry and transfer acetyl and acyl groups, respectively. Pantothenic acid, after passing through several biochemical steps, is converted to CoA, which contains pantothenic acid, adenosine monophosphate, and β-mercaptoethylamine. CoA participates in the synthesis of ACPs. Pantothenic acid is ubiquitous and present in large amounts in many foods, especially liver, kidney, egg yolk, fresh vegetables, royal bee jelly, and tuna and cod ovaries [349]. After CoA hydrolysis, pantothenic acid is liberated and excreted in the urine. Pantothenic acid is currently assessed by radioimmunoassay.

Pantothenic acid is a precursor of CoA, which is necessary for the synthesis of many compounds, including fatty acids, cholesterol, steroid hormones, δ-aminolevulinic acid, and some neurotransmitters and amino acids. CoA is also necessary for energy extraction during the β-oxidation of fatty acids and oxidation of amino acids. Pantothenic acid, as a component of CoA, plays a central role in the acetylation of proteins, microtubules, and histones and in the acylation of proteins (the ACPs) with fatty acids, mainly myristic and palmitic acids. The acetylation and acylation of proteins affect both their structure and activity. In animals, pantothenic acid deficiency results in retarded growth, neuromuscular disorders, abnormalities of skin and hair, and gastrointestinal symptoms. In young men fed a pantothenic-free diet for 9 weeks, their main complaint was fatigue [350]. Several medications may interfere with pantothenic acid metabolism or actions (Table 26.2).

Dietary pantothenic acid intake in chronic kidney disease

Dietary pantothenic acid intake is often reported to be below the RDA when protein intake is 80 g or less per day (Table 26.3; [15]). No data regarding dietary pantothenic acid intake in nondialyzed, advanced CKD, chronic dialysis, and kidney transplant patients are currently available.

Nutritional status of pantothenic acid in advanced chronic kidney disease, chronic dialysis, and kidney transplant patients

There are few data regarding the nutritional pantothenic acid status in kidney failure patients, and the pantothenic acid data in MHD patients are conflictory. Debari et al. [332] found in 12 nonsupplemented MHD patients that pantothenic acid concentrations in plasma, leukocytes, and red cells were significantly higher than in normal controls. Lasker et al. [351] reported normal or high concentrations of pantothenic acid in blood of six MHD and three CPD patients who were not receiving vitamin supplements. On the other hand, Mackenzie et al. [352] reported low concentrations of plasma pantothenic acid in six MHD patients who were not receiving pantothenic acid supplements. Surprisingly, the PROGREDIR study, in a cohort of 373 nondialyzed CKD patients, found a positive relationship between pantothenic acid intake and the score for coronary artery calcification (CAC) measured by computed tomography. Other nutrient intakes (calcium, phosphorus, and potassium) were also associated with the CAC score, whereas others (thiamine, riboflavin, pyridoxine, folate, vitamin B12, vitamin K, niacin, zinc, and selenium) were not [353].

Pantothenic acid supplementation in chronic kidney disease, chronic dialysis, and kidney transplant patients

There are few data on which to base dietary recommendations for supplemental pantothenic acid. Low-protein diets have a reduced content of pantothenic acid. The pantothenic acid clearances with high-flux and/or highly efficient dialysis are unknown. Low concentrations of pantothenic acid have been found in one study in unsupplemented MHD patients [332]. As with biotin, there is no RDA for pantothenic acid in normal individuals, but only an estimation of needs: the AI estimation [348]. Again, because CKD 3−5, MHD, and CPD patients and kidney transplant recipients not uncommonly have low intakes of many nutrients, we suggest that they receive a daily pantothenic acid supplement equal to the AI for pantothenic acid for normal men and normal nonpregnant, nonlactating women, 5 mg/d (Table 26.4). There is no recommendation for pantothenic acid in the recent KDOQI nutrition guidelines other than to encourage CKD 1−5D and CKD T1−5 patients to ingest diets providing sufficient amounts of all vitamins and to consider vitamin supplements to prevent or treat micronutrient deficiencies in individuals with persistently low vitamin intakes [1] (Table 26.4).

Summary:

- The nutritional status of pantothenic acid status in advanced CKD and chronic dialysis patients is controversial.
- Dietary pantothenic acid intake of these patients probably is often below the RDA, and normal, elevated, and low blood levels have each been reported in these individuals.

Continued

- No specific syndromes related to low body pantothenic acid have been reported in CKD patients.
- In the PROGREDIR study, pantothenic acid intake was found to be positively related with the CAC score in nondialyzed CKD patients.
- Because CKD 3−5, MHD, and CPD patients and kidney transplant recipients not uncommonly have low intakes, we suggest that they routinely receive a daily pantothenic acid supplement equal to the AI for pantothenic acid for normal men and normal nonpregnant, nonlactating women, 5 mg/d.

General comments regarding vitamin supplements in kidney disease

In 2001 the KDOQI work group for CPGs for nutrition in chronic renal failure did not address vitamins because of the limited evidence regarding the vitamin needs in kidney failure patients [354]. A few years later a DOPPS report indicated that MHD patients receiving a supplement of vitamins B6, B12, and C, and folates had better nutritional status, as indicated by higher serum albumin levels and nPNA (normalized protein nitrogen appearance), and a 16% decrease in mortality [355]. The reduced mortality persisted after adjustment for nutritional markers. It was not possible to distinguish the specific effects of each vitamin. Vitamin prescription varied substantially across countries, but the impact on mortality did not vary when stratified by geographic regions. The possible explanations for the positive association of improved nutritional status and lower mortality in MHD patients taking vitamin supplements include the plasma Hcy-lowering effects of some of these vitamins, improved patient biochemistry and metabolism due to the vitamin supplements, increased appetite and protein intake with vitamin supplementation, better patient care in chronic dialysis programs where supplements are prescribed, and better socioeconomic status associated with vitamin prescription. However, the prospective trials of Hcy-lowering with vitamin supplements do not support the first hypothesis. Vitamin supplements to prevent deficiency and improve outcomes of renal failure are important issues in these patients, as because morbidity and mortality remain high in this population.

The DOPPS report [355] triggered much interest in water-soluble vitamin supplements for CKD patients. A subsequent small observational study with a 4-year follow-up [356] indicated that water-soluble vitamin supplements have beneficial effects on overall mortality (HR: 0.29; CI, 0.15−0.56). However, since then, no clinical trial or large cohort study has retested the findings from the DOPPS study. The development of new information in advanced CKD and chronic dialysis patients suggesting greater nutritional requirements for vitamin K and challenging the benefits of vitamin E supplements have raised questions concerning the recommendations for fat-soluble vitamins. Finally, it is not unlikely that many CKD and chronic dialysis patients with PEW or protein–energy malnutrition (PEM) may also be deficient in some vitamins. The extent to which concomitant vitamin deficiencies contribute to the adverse outcomes associated with PEW or PEM is unknown. Whether vitamin supplements would be beneficial to CKD or chronic dialysis patients with PEW or PEM is also unknown and would seem worthy of research. Also, the DOPPS report [355] highlighted the wide disparity of vitamin supplementation in MHD patients across countries, from 3.7% in the United Kingdom to 71.9% of MHD and CPD patients in the United States. The varying availabilities of vitamin supplements specifically designed for renal patients, and the absence of strong clinical evidence for a beneficial effect of vitamin supplements, in the face of the not insubstantial costs of routinely providing regular vitamin supplements to advanced CKD and chronic dialysis patients, may account for these differences.

Since then, several guidelines for the nutritional management of kidney disease patients have been published. Some of these propose guidelines on vitamin supplements (see Table 26.4). The CARI guidelines for nondialyzed CKD patients [357] only suggested guidelines for vitamin supplements because of the absence of level I or II evidence. The CARI guidelines state that CKD patients following a protein-restricted diet should receive supplements of thiamine (B1) (> 1 mg/d), riboflavin (B2) (1–2 mg/d), and B6 (1.5–2.0 mg/d of pyridoxine hydrochloride). Steiber and Kopple reviewed the vitamin status and dietary vitamin needs for CKD stages 3–5 patients [358]. The European best practice guidelines [86] recommended for MHD patients 400–800 IU/d of vitamin E based on the SPACE study for the prevention of CV events and the following daily amounts for other vitamins: B1 (1.1–1.2 mg), B2 (1.1–1.3 mg), B6 (10 mg of pyridoxine HCl), C (75–90 mg), folic acid (1 mg), B12 (2.4 μg), niacin (14–16 mg), biotin (30 μg), and pantothenic acid (5 mg). They do not recommend vitamin A supplements but do suggest vitamin K supplements (10 mg/d) for patients undergoing prolonged antibiotic therapy or presenting with bleeding disorders. Tucker et al. [359] commented that the lack of evidence makes it questionable to recommend systematic vitamin supplementation for all MHD patients. However, the authors recognized that in some circumstances, CKD patients will be at increased risk for vitamin deficiencies (e.g., pregnancy, gastrointestinal bypass, anorexia with poor food intake, vegetarian diets, malabsorption states, and the use of some medications), and they may require individualized prescriptions of vitamin supplements.

The recent KDOQI guidelines for nutrition in CKD (Table 26.4) make the general suggestion that for adults with CKD 1–5D and CKD T1–5, a registered dietitian nutritionist or international equivalent should encourage patients to ingest adequate amounts of vitamins in their diet, should periodically assess their dietary vitamin intake, and consider multivitamin supplementation for individuals with inadequate vitamin intakes for extended periods of time [1]. Supplements are suggested for folic acid, vitamin B12, and/or B-complex (i.e., the eight water-soluble vitamins B1, B2, B3, B5, B6, B8, B9, and B12) for adults with CKD 3–5D and CKD T1–5 not only to correct deficiency or insufficiency based on clinical signs and symptoms (Quality of Evidence and Strength of Recommendation: Level 2B), but also in the case of inadequate dietary intake (Opinion) [1]. Folate with or without B-complex supplements is not advised to prevent Hcy-associated adverse CV events, because there is no evidence that the elevated plasma Hcy typically found in advanced CKD or chronic dialysis patients causes such events (Level 1B) [1]. For vitamin C, and stated as "Opinion," supplementation to meet the requirements (75 mg/d in women and 90 mg/d in men) is reasonable for CKD 3–5D and kidney transplant patients [1]. For vitamin A and E, no routine supplementation is indicated. When vitamin A or E supplements are prescribed, patients should be monitored for toxicity (Opinion) [1]. CKD 3–5D and posttransplant patients receiving anticoagulant therapy known to inhibit vitamin K activity should not be prescribed vitamin K supplements (Opinion) [1,360].

There is a paucity of definitive evidence regarding the vitamin needs and the causes, prevalence, and optimal treatment of vitamin deficiencies for these patients. As indicated earlier and in Table 26.4, the many sets of recommendations regarding vitamin supplements for patients with kidney disease are often in conflict with each other. Our recommendations for adults with CKD 3–5D and CKD T1–5 are based on our analysis of the available evidence as well as that of other workers in this field. These recommendations also apply to patients with nephrotic range proteinuria unless stated otherwise. For several vitamins, our recommendations differ from the recent KDOQI CPGs on nutrition in CKD [1] because of our perception that CKD, the uremic syndrome, the dialysis process, and medicinal therapy engender many alterations in the physiology and metabolism of vitamins, including in the intake, intestinal absorption, transport and delivery to tissues, degradation, and biochemical activity of the vitamins. Some compounds that accumulate in kidney failure inhibit the activity of vitamins.

Moreover, we are impressed with the frequency with which advanced CKD and chronic dialysis patients develop acute or chronic intercurrent illnesses or psychological depression which render them anorexic or physically unable to eat a nutritious diet or which further impair the actions of vitamins. As indicated in the previous discussion, the dietary intake of a large number of vitamins have often, although not always, been shown to be below the RDA in CKD 3–5D patients and even in kidney transplant recipients. Moreover, vitamin supplements, if given in appropriate doses, appear to be quite safe. Vitamin supplements for an individual patient are relatively inexpensive. For these reasons, we recommend that CKD 4–5D, kidney transplant 3–5, and often CKD 3 patients should usually be prescribed vitamin supplements. Usually, but not always, the RDA or AI of the vitamin is recommended unless evidence suggests that another dose is more optimal, as indicated earlier, for example, for vitamin B6 (pyridoxine). It is recognized that as research continues in this field, many if not all of the foregoing recommendations may be modified.

Conclusion

It should be evident from the foregoing discussion that the nutritional requirements for many vitamins are not well defined for CKD 3–5D or CKD T1–5 patients, as well as for AKI patients or individuals with the nephrotic syndrome. Indeed, we still do not know the optimal ways to assess the nutritional status for many vitamins in CKD 3–5D patients, kidney transplant recipients and AKI patients. The blood or plasma concentrations of vitamins may be poor indicators of their functional activities. The example of vitamin K in patients with CKD 3–5D highlights the gap that remains between the currently used, rather crude methods for assessing vitamin status and our need for more precise, sensitive and functional methods. [110]. The effects of kidney failure and uremic toxins on the metabolism and actions of vitamins are largely unknown. The DOPPS cohort study suggesting survival advantages associated with water-soluble vitamin prescription must be confirmed in randomized, prospective clinical trials. However, according to the ClinicalTrials.gov website, no such trials are under way, and we are concerned that they might not be conducted, at least in the foreseeable future. In the last two decades, the hope that vitamin therapy targeting hyperhomocysteinemia in advanced renal failure may improve patient outcomes has vanished. The effects of niacin on intestinal phosphorus uptake, phosphate balance and the lipid profile must be more extensively investigated. Data concerning vitamin needs and tolerance in CKD patients, such as, for example, for vitamins A and K, have strongly challenged our traditional concepts. New, forthcoming clinical trials may provide much needed information on the safety and role for VKAs for anticoagulation therapy and whether CKD patients may benefit from vitamin K supplements. Thus many unanswered questions remain, and it may therefore be concluded that the field of vitamin metabolism and nutriture in CKD is wide open for more basic and clinical research.

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CHAPTER

27

Trace elements, toxic metals, and metalloids in kidney disease

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Introduction

Plasma and tissue levels of many trace elements are often altered in patients with acute and chronic kidney diseases (CKDs). Since essential trace elements have important metabolic functions, deficiencies in these elements may lead to either unique syndromes and/or exaggeration of other commonly observed syndromes in patients with kidney disease. Nonessential trace elements and metals may also accumulate in patients with kidney disease and present either with unique clinical syndromes or with other uncertain consequences. In this chapter, we will review the disease processes related to alterations in trace element burden in patients with kidney disease [please see Chapter 8: Catalytic (Labile) Iron in Kidney Disease, and Chapter 38: Nutrition and Anemia in Chronic Kidney Disease, for a more detailed discussion of iron].

Trace elements

Definitions

Trace elements include all naturally occurring elements in the periodic table except the bulk elements and macrominerals. Examples of bulk elements include oxygen, hydrogen, carbon, sulfur, and nitrogen, and their nutritional requirements in humans are in the order of grams per day. Macrominerals include sodium, magnesium, phosphorus, chlorine, potassium, and calcium, and their nutritional requirements usually vary from 1 or 2 g to a fraction of a gram per day [1].

Trace elements are present in the body at less than 0.01% of total body mass, and, if they are essential, their current daily-recommended intake is typically less than 100 mg per day. Ultratrace elements are typically defined as those with a daily requirement of less than 1 mg per day.

Trace elements may be differentiated between those with or without established essentiality, and their source is usually from air, water, or diet. Withdrawal or the absence of essential trace elements from the diet will produce functional or structural changes that are usually reversible upon the replacement of the deficient element. Although all of the trace minerals important to human nutrition are elements, they are not all metals (e.g., selenium and iodine). A metalloid is a chemical element with properties in between a metal and a nonmetal. Commonly recognized metalloids include arsenic, antimony, boron, germanium, silicon, and tellurium.

Trace element functions

Trace elements serve three broad physiologic functions: (1) oxygen binding and transport; for example, iron (Fe); (2) metabolic catalysis; for example, manganese (Mn), molybdenum (Mo), copper (Cu), zinc (Zn), selenium (Se), and chromium (Cr); and (3) hormonal effects; for example, Se and iodine (I). In addition, the roles of certain micronutrients, especially Fe, Zn, and Cu, are increasingly being recognized for their role in regulating innate immunomodulation and for making a pivotal contribution to the protection against bacterial, mycobacterial, and fungal infections, leading to the concept of “nutritional immunity.” Host cells work through mechanisms of creating a scarcity of these micronutrients as well as flooding the area with them

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when needed [2–6]. Located on cellular transmembrane interphases, Toll-like receptors (TLRs) recognize pathogens when activated by their ligands. The activating factors include vitamins and such trace elements as iron, copper, and zinc [7]. Environmental factors, the geographic region, topsoil, water, and dietary habits play a significant role in determining plasma and tissue concentrations of trace elements in the body [8].

Overview of trace elements in kidney disease

Papers dating back to the 1970s described trace element–related disorders in chronic dialysis patients. Trace element deficiencies, such as zinc and selenium, were recognized in dialysis patients, and oral intake and use of tap water for dialysate were identified as sources of trace element contamination and toxicity [9]. As an example, silicon toxicity was discovered with plasma levels to be almost 100-fold higher in dialysis patients. It was determined that the water used for dialysis preparation was the likely source of toxicities [9]. It also became apparent that the process of dialysis might lead to deficiencies. Aluminum, silicon, copper, zinc, nickel, strontium, and chromium were all shown to have the potential for transfer from dialysate to the patient resulting in toxicity. This led to recommendations for water purification using reverse osmosis technology and for strategies to chelate certain trace elements with deferoxamine, particularly for aluminum toxicity, when indicated [9,10].

Data also emerged regarding the role of trace element toxicity or deficiency as a cause of kidney disease and as a mechanism that may worsen the clinical course of established CKD. As an example, increased levels of phosphorus and copper, and decreased zinc can promote further worsening of CKD and the associated vascular complications through oxidative stress and tissue injury [11].

It is uniquely challenging to assess accurately the accumulation or deficiency of trace elements in CKD patients because of significant changes in the physiologic milieu and the body distribution of some trace elements [12]. Commonly, trace element burden is assessed by serum or plasma measurements; however, plasma trace element levels may not reflect the actual total body stores, because the uremic milieu and the compromised kidney physiology result in preferential excretion or retention of different elements. Further, removal during dialysis, the quality of water used during dialysis, as well as increased urinary loss in kidney transplant patients can all affect measurements [13]. Even brief exposure to renal replacement therapy in the setting of acute kidney disease can impact levels. In a recent study of patients with acute kidney injury (AKI), Ostermann and colleagues demonstrated that serum levels of zinc, copper, and selenium were lower in more than 30% of patients with AKI, irrespective of whether they were or were not receiving continuous renal replacement therapy (CRRT) [14]. In patients undergoing CRRT, severe deficiencies of selenium and copper have been reported. Thus selenium deficiency observed in critically ill patients may become further worsened by CRRT [15]. Low copper was associated with bradycardia and hypertriglyceridemia. Serum rubidium levels decrease significantly during hemodialysis, because there is little or no protein binding of this element and, hence, it is readily dialyzed. The clinical implications of rubidium removal or low serum rubidium are unclear. There is also a surprising increase in serum levels of chromium, cobalt, molybdenum, and manganese in patients undergoing CRRT [15]. Collectively, these studies demonstrate the importance of close monitoring of trace elements needed in patients undergoing CRRT and the importance of appropriate supplementation.

Important changes in serum trace element levels have also been observed in patients with end-stage renal disease (ESRD), and these changes may be associated with adverse outcomes. In a recent study, Tonelli and colleagues observed that lower serum selenium concentrations were strongly and independently associated with the risk of hospitalization and death in maintenance hemodialysis (MHD) patients [16].

Some caution is required in interpreting these studies, as there may be temporary or associated redistribution of these elements during inflammatory states and associated acute-phase response, making plasma or serum values particularly unreliable indicators of body trace element burden [17]. There are also limitations to the methodology of the laboratory testing. Being present in such small quantities, measurements of these elements need great care during collection and processing of specimens. Furthermore, there is a significant risk of contamination that may even occur from the instruments used for the trace element measurements [18].

We will first focus on essential trace elements and then discuss nonessential trace elements and metals in patients with kidney disease.

Alterations in essential trace elements in patients with chronic kidney disease

The current literature on alterations in individual essential trace elements in kidney disease will be reviewed and presented in the order of potential importance and available evidence.

Zinc (Zn)

Zn distribution

Zn is found in all body tissues with the majority in muscle and bone (85%), followed by the skin and liver (11%), and the rest in other tissues. Body Zn is situated mostly intracellularly. Zn is distributed between the nucleus and the cytoplasm, and in smaller amounts in organelles, vesicles, and the cell membrane. Zinc enters the human body by three known routes: inhalation, absorption through the skin, and by ingestion [19].

Zinc can be obtained from major protein sources, including oysters, poultry, meat, eggs, and whole cereal grains, as well as from fortified foods [20]. The National Institute of Health's Office of Dietary Supplements fact sheet for health professionals provides recommendations and guidelines of the Dietary Reference Intakes developed by the Food and Nutrition Board. This fact sheet provides reference values that can be used for assessing the adequacy of nutrient intakes of normal people [20]. The Recommended Dietary Allowance for zinc in adults is 8 mg per day for normal, nonpregnant women and 11 mg per day for normal men. These recommendations are not directed to the CKD population, and a wide variation is seen in supplementation doses. A metaanalysis reported supplemental elemental zinc doses ranging from 11 to 100 mg for different populations [21]. Zinc is absorbed in the duodenum and proximal jejunum and is transported by apical membrane transporters through enterocytes and circulated to the tissues as protein-bound Zn [22].

Zn functions

Zinc has an essential role through zinc-containing enzymes and proteins in catalytic, structural, and regulatory functions that affect metabolism, gene expression, and signal transduction [23]. Some of these processes prevent oxidative stress. As noted earlier, Zn plays a significant role in immunity and host defenses. Zn can act as a signaling molecule in signaling cascades, such as in the activation of TLRs [7]. Deficiency of zinc transporter ZIP7 results in impaired B-lymphocyte development and humoral immune deficiency [24]. Zinc transporter, ZIP10, appears to be important for B-cell receptor signaling [25]. Zinc was recently shown to protect against uropathogenic *Escherichia coli* infections [26].

Zinc plays a critical role as a cofactor for many enzymes that regulate a wide variety of cellular activities (e.g., alcohol dehydrogenase, alkaline phosphatase, angiotensin-converting enzyme, and superoxide dismutase). Zinc is an important component of zinc finger proteins that act as transcription factors that allow binding of proteins to deoxyribonucleic acid (DNA) and that control gene expression [27]. In addition, serum zinc-alpha2-glycoprotein, an adipokine associated with cancer cachexia, is found to be increased in CKD patients. This adipokine appears to predict clinical outcomes independently, including cardiovascular events and mortality, in MHD patients [28].

Zinc is also known for its role in skeletal growth; zinc appears to stimulate osteoblastic bone formation and inhibit osteoclastic bone resorption [29]. Zn is known to play a significant role in wound healing [30].

Bioinformatic processes, including proteomics and genomics, show there are over 3000 unique human zinc proteins, implying that about 10% of the human genome may involve encoding of zinc proteins. There are multiple mechanisms in place to maintain intracellular zinc concentration, highlighting its importance in normal body physiology and also its dynamic regulation within the cell. Disruption in this homeostasis may result in increased oxidative stress and subsequent kidney damage [31].

Zn measurements

The measurement and interpretation of plasma zinc levels are especially challenging, because plasma levels can be depressed during inflammation and hypoalbuminemia and can be increased postfasting and in catabolic states. Despite this caveat, plasma measurements are preferred over serum due to the lack of erythrocyte contamination. Alternative indirect or secondary markers of the adequacy of body zinc content may include erythrocyte zinc concentrations, activity of such zinc-dependent enzymes as alkaline phosphatase or erythrocyte or monocyte metallothionein, the family of zinc transporters, and gene markers [32].

Zn toxicity

Ingestion is the primary mode of entry of Zn into the body. Toxic inhalation of Zn can cause pulmonary injury; Zn absorption through skin that may result in systemic effects is rare. Acute intoxication due to exposure to large quantities of Zn is rare. The at-risk populations for chronic toxic Zn exposure are the people working in the metal industries, especially welding. As with some other toxic trace metals, environmental Zn pollution, including Zn contamination of soil, can contribute to rapid worsening of kidney disease in CKD patients [33]. Zinc excess in the body may cause rough hair, diarrhea, microcytic anemia, and hypercholesterolemia. Since zinc competes with copper, manganese, and iron for intestinal absorption, excessive oral zinc intake may lead to copper, manganese, or iron deficiency [34].

Zn deficiency

Zn deficiency usually is a more common occurrence than Zn excess in people with chronic disease states such as kidney failure, kidney transplantation, anorexia, malnutrition, and the elderly [23,35]. The mechanisms leading to zinc deficiency include decreased dietary intake, intestinal malabsorption, and losses into dialysate or urine. Zn absorption from the intestinal tract and Zn excretion can be affected by certain medications as well as by phytates in food which may decrease intestinal Zn absorption [36,37].

Marginal zinc intake may be associated with an increased risk of cardiovascular disease in the general population. In animal studies, zinc has been shown to be protective against atherosclerosis by inhibiting the oxidation of low-density lipoprotein cholesterol [38]. Zn deficiency in experimental animals is reported to increase oxidative stress and NF-κB DNA-binding activity and to induce inflammation [39–41]. Zn is essential for insulin synthesis and release and for glucose homeostasis [42]. Data suggest that Zn deficiency may impair insulin secretion and decrease serum leptin levels [43].

Alcoholism, medications such as hydrochlorothiazide, penicillamine, and ethambutol, sickle cell disease, human immunodeficiency virus infection, and liver and kidney disease are associated with zinc deficiency. In the general population, zinc deficiency is manifested by growth retardation, poor wound healing, decreased sexual performance, abnormal hair and nails, loss of taste (hypogeusia), such gastrointestinal (GI) disorders as anorexia, abdominal pain, nausea, and glossitis, and impaired folate and vitamin A absorption. Zinc is also important for neurobehavioral function, and Zn deficiency can result in increased anxiety and depression [44–46].

Zn in kidney disease

The dietary restrictions that are commonly prescribed for CKD patients, which include a moderate-to low-protein diet also low in potassium and phosphorus, increase the risk of zinc deficiency, because the foods low in these nutrients are often also low in many other trace elements [47,48]. Zinc deficiency may progressively worsen in advanced CKD and chronic dialysis patients, and studies in experimental animals suggest that zinc deficiency may enhance progression of kidney failure [31].

Zn and chronic kidney disease In a study from Korea, lower than recommended mineral intakes, including zinc, were more likely in advanced stages of CKD [49]. A study from Taiwan in type 2 diabetic patients with early CKD (Stages 1–3b) indicated a significant trend toward decreasing serum levels of zinc and iron. This was considered to probably be due to hyperglycemia-induced glycation of basement membrane protein, leading to a loss of charge selectivity with glomerular hyperperfusion and hyperfiltration and urinary trace element losses [50].

Low baseline zinc has been correlated with a more rapid decline in kidney function. Moreover, the mean plasma zinc levels in CKD stage 5 patients were 18% lower than in non-CKD patients. The trend for plasma zinc levels to decrease with loss of glomerular filtration rate was associated with an increase in urinary fractional excretion of zinc. The mechanism for this dysfunctional handling of zinc may be related to progressive tubular injury [51] and its effect on the tubular zinc transporters, ZIP8 (SLC39A8) and ZIP14 (SLC39A14), which can also mediate iron absorption and deposition [52].

Zinc deficiency may lead to the progression of the disease through multiple mechanisms, including increased reactive oxidative damage and kidney hyperfiltration and worsening proteinuria. In addition, zinc deficiency may promote vascular calcification induced by hyperphosphatemia; this process is regulated by the transcription factor NF-κB as has been shown in an animal model and an in vitro study [53]. The findings from these studies also indicate that supplementation may reverse zinc deficiency–induced damages and may represent a possible therapeutic option for CKD patients [31,54].

Zn and hemodialysis The mean plasma zinc level, the mean GI absorption, and the mean half-life of zinc are reported to be lower in MHD patients as compared to healthy controls [55]. Dietary zinc intake was normal and did not correlate with plasma zinc, leukocyte zinc, or GI zinc absorption [55]. Lower serum zinc in advanced CKD and chronic dialysis patients may also be related to altered zinc binding to serum proteins. Serum zinc measurements may need to be correlated with serum albumin similar to the way that serum calcium is often adjusted for serum albumin. When serum zinc levels were normalized according to the serum total protein or albumin levels, a significant association was observed between serum zinc and taste impairment in MHD patients [56].

Many MHD patients suffer from zinc deficiency [57–59] (Table 27.1). In one study, 96% of anemic dialysis patients were found to be zinc deficient, based on serum zinc measurements [60]. In patients with serum zinc levels less than 80 μ/dL, the anemia responded favorably to oral zinc supplementation. In particular, many patients who were receiving erythropoietin (EPO) therapy and diagnosed with refractory anemia had zinc deficiency anemia. Zinc replacement not only corrected the anemia but also substantially lowered the EPO requirements in these patients. Thus zinc deficiency anemia should be considered in chronic dialysis patients who are EPO resistant [60].

Zn and peritoneal dialysis Zinc deficiency is a concern for chronic peritoneal dialysis (CPD) patients, especially since they may have higher losses through

TABLE 27.1 Zinc metabolism in kidney disease.

- RDA for zinc for normal men, 11 mg per day, and normal nonpregnant women, 8 mg per day
- Foods with high zinc content: oysters, poultry, meat, eggs, legumes, and whole-grain cereals
- Function: cofactor for many enzymes, zinc finger proteins
- Specific clinical manifestations of deficiency in maintenance dialysis patients: erythropoietin resistance, anxiety, depression, dysgeusia, and hyperammonemia
- Diagnostic laboratory tests: decreased serum zinc levels, low serum alkaline phosphatase (suggestive)

RDA, Recommended dietary allowance.

the peritoneum and stool. In a study of stable CPD patients, the incidence of zinc deficiency was as high as 57.2% [61]. However, Tamura et al. reported the presence of zinc in commercially available PD dialysate, and this zinc was lower in the effluent dialysate, implying significant zinc absorption through the peritoneum during dialysis [62]. Conversely, Mahajan et al. showed that although their patients undergoing continuous ambulatory peritoneal dialysis (CAPD) also had zinc deficiency, they noted a loss of zinc into peritoneal dialysate in their patients. They also reported that episodes of peritonitis were associated with the lowering of serum zinc levels. Data in PD patients are limited compared to HD patients [63].

Zn and continuous renal replacement therapy Trace elements can significantly be cleared by CRRT. A retrospective analysis shows that, of the micronutrients measured (thiamin, pyridoxine, ascorbic acid, folate, zinc, and copper) during CRRT in 75 patients, 80% of the 75 were deficient in at least one micronutrient [64]. Prolonged CRRT can cause significant losses of selenium, copper, zinc, and thiamine from serum leading to measurable depletion of these micronutrients [15,65,66].

Zn and kidney transplantation Early studies showed that Zn deficiency persists after kidney transplantation in some patients [35]. Serum zinc levels also correlate with selenium levels [67]. Immunosuppressant drugs used in kidney transplant patients, such as mycophenolate mofetil (MMF), may affect serum levels of some trace elements. MMF is known to increase serum copper levels in transplant recipients, increase serum copper and iron in women especially, and decrease selenium level in patients younger than 50 years old. MMF increases Se level in the blood of transplant recipients when used in combination with prednisone [68].

Zn supplementation

Four short-term randomized control trials (RCTs) examined the effect of oral zinc supplementation on serum lipid levels [69–72]. Argani et al. and Rahimi-Ardabili et al. administered, orally, 100-mg zinc daily to MHD patients for 2 months [69,71]. Argani et al. reported that zinc supplementation did not change serum cholesterol or triglyceride levels [69]. Rahimi-Ardabili et al. reported that serum cholesterol levels increased significantly in the placebo group but did not change in the treatment group, and that serum cholesterol levels at the end of the intervention period were not different between the two groups [71]. In other studies, Roozbeh et al. [72] and Chevalier et al. [70] supplemented MHD patients with 50-mg zinc daily for 6 weeks and 90 days, respectively. All patients in these two studies had low serum zinc at baseline (<80 μg/dL). Total cholesterol, LDL-C, HDL-C, and serum triglyceride levels increased in the zinc-supplemented group, and there was no change in the control group [70,72].

Pakfetrat et al. demonstrated that 50 mg of oral zinc per day for 6 weeks in MHD patients significantly decreased serum homocysteine levels as compared to the MHD patients assigned to the placebo group [73]. A study reported an association between low serum zinc levels and depression in MHD patients [74]. However, there are no well-conducted studies that have examined whether zinc treatment will improve depressive symptoms in MHD patients. Zinc deficiency in MHD patients may also result in hyperammonemia, because ornithine transcarbamylase is a zinc-dependent enzyme; these abnormalities are well corrected with zinc treatment [75].

Two other studies examined the effects of zinc supplements on inflammatory markers; the results were inconclusive. Data on the effects of zinc supplementation on body weight and BMI also gave mixed results [69,76]. In MHD patients with normal or low bone turnover, a single-center study from Japan found a positive effect of zinc supplements on bone formation independent of parathyroid hormone (PTH) and vitamin D [77].

Several clinical studies examined the effect of zinc supplementation on serum zinc levels in MHD patients [34,69–72,76,78]. The dose of the zinc supplements ranged from 11 to 110 mg per day, and the study duration ranged from 5 weeks to 6 months. A pooled analysis of these studies showed a mean increase in serum zinc of 30.97 μg/dL (95% confidence intervals, 17.45, 44.59) after supplementation as compared to the control group, but there was high heterogeneity. There is evidence that low-dose zinc supplements do not correct low-zinc status in the MHD population [78]. However, it is not firmly established whether zinc supplementation affects any clinical outcomes in CKD patients.

A small study from Japan reported a decrease in left ventricular end-diastolic size after 3 months of concomitant zinc and selenium supplements in 18 MHD patients. The MHD patients also exhibited an increase in natural killer-cell activity—a vital host response to infected cells. Investigators used a formula that contained 50 μg of Se and 12 mg of Zn, along with other nutrients, including protein and 12 vitamins and 10 minerals, once daily for 3 months [79]. It should be emphasized that the long-term benefits or toxicity of zinc supplements, and the doses of zinc supplements at which these effects might occur are unknown. Chronic zinc supplementation can induce copper deficiency [80].

Copper (Cu)

Cu distribution

Copper (Table 27.2) exists in the body in two oxidative states, as the cuprous (Cu^{+}) and cupric (Cu^{2+}) ions. The normal adult human body contains about 50−120 mg of copper, with the highest content in the liver (10−35 μg/g of dry weight). Copper is primarily excreted via bile (2 mg/day), and normally about 10−50 μg of copper are excreted daily in the urine. Ceruloplasmin is the major copper-binding protein in the blood and in plasma; 60%−90% of the copper in plasma is bound to ceruloplasmin, and the remainder is loosely bound to albumin. The normal plasma copper level is about 0.75−1.45 μg/mL, and plasma ceruloplasmin levels are 190−510 μg/mL. In the Western diet, 60% of dietary copper comes from vegetable sources (grains, nuts, and chocolates), and 20% is derived from meat, fish (particularly shellfish), and poultry [81]. Recommended daily intake for copper is about 340 μg for children to about 900 μg for adults. Copper is absorbed in proximal small intestine and stomach. Acidic environment of stomach facilitates absorption by dissociation of copper from complexed macromolecules. Dietary absorption of copper can be impaired by iron, zinc, or ascorbic acid.

Cu functions

Copper serves as a cofactor for many enzymes, known as cuproenzymes. Copper is essential for the function of several well-known enzymes, including superoxide dismutase [Cu/Zn superoxide dismutase (SOD) is an antioxidant], amine oxidase (monoamine oxidase), lysyl oxidase (involved in collagen synthesis), tyrosine hydroxylase, dopamine beta-hydrolase (involved in skin pigmentation), factor V (for coagulation), and cytochrome *c* oxidase. Cu/Zn SOD has two atoms of copper per molecule and is present at high levels in the brain and kidney, among other tissues. Copper plays an additional important function in iron metabolism, which is mediated through ceruloplasmin or ferroxidase. Cu has a pivotal role in immunomodulation combating infections [5]. Innate immune cells utilize Cu through different pathways to achieve an effective interface to protect the host. These processes include the regulation of Toll-like receptors and the compartmentalization or sequestration of infected cells [4,6].

Cu measurements

For clinical purposes, copper has been measured using some direct measurements like serum and plasma-free Cu levels, and also through various correlations such as ceruloplasmin concentrations, erythrocyte superoxide dismutase activity, and platelet Cu concentration. Historically, plasma Cu levels were estimated by a calculation that assessed the copper index or nonceruloplasmin-bound copper. However, this process was not very accurate, and currently most laboratories directly measure copper concentrations.

Copper measurements are helpful in states of clear deficiency but are not helpful if there is a suspicion of moderate reduction in copper intake or moderate deficiency. In pregnancy and such diseases as rheumatoid arthritis, leukemia, lymphoma, or primary biliary cirrhosis, plasma ceruloplasmin levels can increase, thus making copper measurements less accurate indicators of deficiency or excess in individuals with these conditions. Platelet copper concentrations and cytochrome *c* oxidase activity may be more sensitive indicators of marginal dietary copper intake or copper deficiency [32]. Cu is commonly measured in serum or plasma by quantitative inductively coupled plasma-mass spectrometry in reference labs [82].

TABLE 27.2 Copper metabolism in kidney disease.

- RDA for copper for normal men and normal nonpregnant women: 900 μg per day
- Major dietary sources: nuts, chocolates, meat, and shellfish
- Function: cuproenzymes, collagen synthesis, and iron metabolism
- Specific clinical manifestations of deficiency in maintenance dialysis patients: erythropoietin resistance, anemia, neutropenia, and neurodegenerative illness
- Risk factors for deficiency: bariatric surgery, zinc supplementation, and parenteral nutrition
- Laboratory tests to diagnose copper deficiency: low serum copper and ceruloplasmin levels; serum ferritin may be high
- Copper accumulation: historic, in patients dialyzed with cuprophane membrane; link to dialysis-related amyloidosis

RDA, Recommended dietary allowance.

Cu toxicity

Copper toxicity, though rare, does occur. The route of intoxication can vary—most commonly by oral intake through suicidal intent, indigenous medications, and practices such as boiling milk in copper vessels, herbal medications, alternative medical practices, or supplementation [83]. An Italian study reported increased intake of copper, as compared to other trace elements, in a cohort of MHD patients [84]. Copper toxicity can also happen through an intravenous administration [85], transcutaneous absorption via wounds or chemical burns [86], intrauterine (e.g., for abortion), and also by the intrarectal route, as described in an unusual case report where the patient used it to treat infertility [87].

Copper sulfate toxicity can present with GI symptoms, including bleeding, hepatotoxicity, kidney failure, and multiorgan failure. There may be a role of serum alanine aminotransferase and aspartate aminotransferase measurements for identifying patients at higher risk of mortality (sensitivities of 100% and 85.7%, and specificities of 73.1% and 69.2%, respectively, for peak serum alanine aminotransferase levels greater than 55 U/L, and peak serum aspartate aminotransferase levels greater than 234 U/L) [88].

Cu deficiency

Several minerals influence copper absorption from the GI tract. Dietary zinc, in particular, can decrease copper absorption through the stimulating effects of zinc on metallothionein synthesis and the subsequent binding of copper by metallothionein. Excess dietary iron also can decrease copper absorption. In patients undergoing CPD, loss of ceruloplasmin-bound copper into the dialysate may lead to copper deficiency. People who have proteinuric kidney diseases may have increased urinary copper losses that may also contribute to copper deficiency. Thus previous bariatric surgery, malabsorption, zinc supplements, proteinuria, and CPD serve as risk factors for copper deficiency.

Copper deficiency in the general population is characterized by fragile, abnormally formed hair, depigmentation of the skin, myeloneuropathy, ataxia, edema, osteoporosis, and hematologic changes (microcytic anemia and neutropenia) (Table 27.2). Neurologic manifestations due to copper deficiency may be precipitated in patients who have undergone bariatric surgery [80] and those who are receiving dietary zinc supplements [89].

Cu and kidney disease

Cu and acute kidney injury Excess copper intake can cause a syndrome of hemolysis and AKI [90]. The intravascular hemolysis is associated with methemoglobinemia. Acute copper toxicity may cause acute tubular necrosis; tubulointerstitial nephritis and rhabdomyolysis [91].

Cu and dialysis treatment Copper accumulation has been described historically in patients who received hemodialysis with a cuprophane membrane, which is a cellulose membrane prepared by the cuprammonium method that contains small amounts of copper [92,93]. Studies have shown a potential contributory role for copper in the genesis of β2-microglobulin amyloidosis (also known as dialysis-induced amyloidosis) [94].

Klein et al. had reported cases of hemodialysis-induced severe copper poisoning presenting with hemolytic anemia due to the contamination of dialysate by oxidative release by heat and acid of copper in the dialysis heating coils [95]. Over the following years, equipment manufacturers eliminated copper tubing from dialysis machines, and stringent monitoring of the pH and conductivity became the standard of care. However, this route of copper toxicity is still a concern. Modern plumbing systems commonly incorporate backflow prevention devices that are made from brass. The ultrapure water needed for preparing incenter dialysate is highly corrosive and carries the potential to leach copper and zinc from these devices. The Association for the Advancement of Medical Instrumentation, a national organization that develops standards and promotes safe, effective use of medical instrumentation and related technologies, continues to work with the International Association of Plumbing and Mechanical officials to address these concerns. An amendment to the existing codes was proposed to designate the dialysis water system, including all of its plumbing components, as a medical device. The amendment also proposed that backflow prevention devices not be needed at the inlet of each dialysis machine. However, there is certainly a requirement for backflow prevention at the inlet to the dialysis water system [95–97]. Copper toxicity is usually treated with chelation (e.g., D-penicillamine or trientine) or zinc supplementation.

Copper deficiency may be present and remain underdiagnosed in chronic dialysis patients [47,98–101]. Symptoms of copper deficiency described in maintenance dialysis patients include neutropenia [102], EPO-resistant anemia [103], bicytopenia (the combination of anemia and neutropenia) [104], and neurodegeneration (cerebellar, spinal cord, and peripheral nerve disorders) [80].

An MHD patient with copper deficiency was presented with ataxia and paresthesias and had magnetic resonance (MR) imaging that displayed an image indistinguishable from subacute combined degeneration of the spinal cord. The copper deficiency was considered to be secondary to chronic zinc supplementation [105].

Ceruloplasmin-related indexes were reported to show moderate Cu deficiency in CPD patients. However, this was not confirmed by erythrocyte SOD activity or mononuclear cell copper measurements [99].

Significant losses of copper and selenium into the effluent dialysate can occur during CRRT. This is especially likely to occur in patients who receive prolonged CRRT for AKI. A patient who received CRRT for 180 days developed copper deficiency with the life-threatening symptoms of bradycardia and hypertriglyceridemia [66].

The treatment of copper deficiency usually consists of oral copper supplementation. In patients receiving total parenteral nutrition (TPN), intravenous copper replacement may be necessary, particularly if the TPN is given for an extended period.

Changes in the metabolism and serum levels of copper and zinc occur simultaneously in kidney transplant patients. The literature has been covered previously in the “Zn and kidney transplantation” section.

Manganese

The total amount of manganese (Mn) in the adult human body is about 12–20 mg. Of the organs, bone and the kidney have some of the highest concentrations of manganese. Within the cell, it is concentrated in the mitochondria and the nucleus. Manganese is a key component of metalloenzymes. Manganese is important in the formation of cartilage, in glucose metabolism, and in the activities of enzymes, such as arginase and manganese superoxide dismutase (which has antioxidant function). Dietary sources of manganese include whole-grain cereals, fruits, and vegetables. After intake, Mn is sequestered to body tissues, thus making plasma level measurements unreliable for assessing exposures or toxicity. Measurements of Mn in red blood cells or whole blood give a more reliable estimate of the adequacy of the body Mn content rather than plasma levels; thus most studies use whole blood Mn levels [106].

In CKD patients, blood Mn concentrations correlate positively with serum hemoglobin levels. Higher blood Mn levels are independently associated with a decreased risk of anemia in CKD patients [107]. There may be an association between worsening CKD and blood Mn levels [108,109].

Low blood Mn levels were associated with an increased prevalence of diabetes and kidney disease in a large prospective Korean study, suggesting that blood Mn deficiency might be involved in the pathophysiological processes of diabetes and diabetic nephropathy [108]. Some data indicate that higher blood pressures may be correlated with higher Mn levels [110]. Blood manganese levels are often low in MHD patients [58]. Serum manganese concentrations correlate with the protein–energy status in MHD patients [111]. A study showed an association between low serum manganese levels and increased carotid atherosclerosis in MHD patients [112]. In some MHD patients, serum manganese levels are increased and also exhibit deposition of manganese in the cerebral basal ganglia, which are visualized as hyperintense signals on T1-weighted MR images. These patients may present with extrapyramidal syndromes, Parkinsonism, myoclonus, and vestibular auditory syndromes [113].

Selenium

Selenium (Se) is an essential trace element that is important for controlling oxidative stress, by modulating glutathione peroxidase (GPX) activity, which is an important defense against iron-mediated lipid peroxidation and ferroptosis (a programmed cell death that is dependent on iron and is characterized by the accumulation of lipid peroxides), immune function, and thyroid hormone synthesis [114]. In the kidney, selenium appears essential for the function of GPX4, a critical enzyme that protects the kidney from ferroptosis and AKI [115]. Selenium deficiency has been found to be associated with bone disease (endemic osteochondropathy or Kashin–Beck disease) and cancer and may increase the risk of cardiovascular diseases [116]. Keshan disease is an endemic cardiomyopathy due to selenium deficiency that is seen in parts of China where the soil is deficient in selenium [116].

Se supplementation improved cellular GPX activity in patients with different stages of CKD [117,118]. Serum selenium levels are often decreased in MHD patients [47,114], and serum selenium levels correlate with the patient’s protein–energy status [114]. Correction of selenium deficiency results in increased GPX activity with a potential reduction in oxidative stress [119] and is also shown to reduce DNA damage [120]. Omrani et al. showed that selenium supplementation does not have any significant effect on thyroid function tests, acute phase reactants, or the lipid profile in MHD patients [118].

In a population-based cohort study of 1040 MHD patients, the quartiles of serum selenium levels were inversely associated with death risk. Particularly notable was the increase in death associated with infectious complications in patients who had the lowest serum selenium concentrations [121]. Decreased serum selenium levels in MHD patients may be associated with increased cardiovascular risk [122]. In addition, lower serum concentrations of selenium in MHD patients are independently associated with the risks of hospitalization and death [16].

Selenium may also have a protective effect against vascular calcification [122]. The content of food selenium can depend on soil selenium levels. However, a study that compared MHD patients living in areas of Brazil with high soil selenium content (north Brazil, Amazon soil) versus low soil selenium (southeast Brazil) found that, independent of region, MHD patients have low serum selenium levels [123].

Supplementation with Brazil nuts (the richest known food source of selenium) corrects selenium deficiency in MHD patients [124]. Whether ingesting Brazil nuts will reduce oxidative stress and inflammation in MHD patients was studied in a prospective, uncontrolled 3-month clinical trial. The trial was conducted to determine whether the beneficial effects for MHD patients of taking one Brazil nut per day for 3 months would be sustained 12 months after cessation of the Brazil nut intake. Total 29 MHD patients (58.6% men, 51.0 ± 3.3 years) in Rio de Janeiro, Brazil, were evaluated 12 months after the supplement study had ended. Plasma levels of such antioxidant substances as selenium, GPX, 8-isoprostane, 8-hydroxy-2-deoxyguanosine (8-OHdG), and the cytokines, tumor necrosis factor alpha, and interleukin-6 were measured before, after 3 months of supplementation, and after 12 months. After 3 months of supplements, the plasma cytokine, 8-OHdG, and 8-isoprostane plasma levels had decreased, and plasma activity of GPX and selenium had increased. These changes were statistically significant. At 12 months the plasma values of 8-isoprostane, 8-OHdG, and cytokines had significantly increased and the plasma activity of GPX and selenium was significantly decreased. These data indicate that these biomarkers of oxidative stress and inflammation biomarkers 12 months after cessation of the Brazil nut treatment were increased as compared to the baseline as well as compared to 3-month levels. Hence, it would seem that to attain a sustained beneficial effect, it is necessary to motivate patients to continue to take the Brazil nuts [124].

Selenium toxicity or selenosis is rare and is manifested by brittle hair, breath with a garlic-like odor, GI symptoms such as nausea, vomiting, diarrhea and, rarely, acute tubular necrosis [125].

Boron

Boron, the fifth element in the periodic table, is ubiquitous in nature. Boron in humans is mostly present in the bone and seems essential for the structure of bone [126,127]. Boron is beneficial particularly to bone and mineral metabolism in the setting of vitamin D deficiency [128,129]. This may be particularly relevant to CKD and chronic dialysis patients who commonly exhibit significant vitamin D deficiency. Exposure to boron has been implicated as a cause of AKI as well as a potential cause of CKD in Southeast Asia [130]. Hemodialysis treatments substantially decrease serum boron levels [131]. The consequences of boron deficiency are unknown.

Chromium

Chromium (Cr) is an essential element. Its primary role appears to be the enhancement of insulin sensitivity at the muscle cell level, which is mediated through a binding protein known as chromodulin. Chromium deficiency, thus, can result in insulin resistance. The recommended daily intake is about 30–35 μg per day. Rich dietary sources of chromium include egg yolks, meat, and whole grains [132].

The effects of chromium deficiency on patients with kidney disease still need to be investigated. Chromium toxicity, on the other hand, has been implicated as a cause of kidney diseases, including acute tubular necrosis and chronic interstitial nephritis, and as a cause of proteinuria. Chromium toxicity is considered an occupational hazard in chromium workers (platers and welders). The diagnosis of chromium toxicity is helped by a high index of suspicion. A history of occupational exposure may offer a clue to diagnosis. With hemodialysis and supportive care, it is a potentially salvageable condition [133].

A 21-year-old man, a worker in a mobile phone shop, was admitted with rhabdomyolysis, kidney failure, and pulmonary edema requiring mechanical ventilation and hemodialysis. After extensive workup and ruling out of other causes, heavy metal poisoning was considered. Investigations during the course of the hospital stay revealed inadvertent chromium poisoning. With repeated hemodialysis, his condition improved, and he was discharged home in a stable condition [133]. A study from Taiwan reported that the decline in kidney function due to lead and cadmium was enhanced with coexposure to chromium [134]. Cr toxicity has been suggested as a possible cause of CKD of unknown origin [135].

Measurement of Cr, like other metal ions, needs a consideration of the valency, as there is a difference in effects of different valencies. Cr(VI) ion, known to be carcinogenic and cytotoxic, can easily be transported across cells and is associated with oxidative stress due to the reduction to Cr(III) in vivo, whereas the Cr(III) ion may be beneficial [136]. Serum Cr was found to be higher than in CPD patients than MHD patients possibly due to the absorption of chromium from peritoneal dialysate [137], although a decrease in serum chromium levels using typical peritoneal dialysate solutions have also been reported [138].

Fluoride

Fluoride is an essential trace element that is important for dental and bone health. Fluoride is one of the most powerful known oxidants. Serum and bone fluoride content are generally increased in patients with reduced kidney function [139]. In a recent study, fluoride accumulation was thought to contribute to the pathogenesis of endemic CKD of unknown etiology (CKDu) [140]. Toxic effects of fluoride have been described in osteoblasts [141] in chronic dialysis patients; however, no causal relationship with osteomalacia and high levels of deposition of fluoride in bone of MHD patients could be established [142]. Acute fluoride intoxication in MHD patients due to the contamination of dialysate water has been reported.

These patients manifested severe pruritus and, in some patients, fatal ventricular fibrillation [143]. The mechanisms of these fatal toxic effects include the induction of profound hypocalcemia, inhibition of $Na^+-K^+-ATPase$, and development of an explosive hyperkalemia [144].

Cobalt

Cobalt is an essential component of vitamin B_{12}. In the past, cobalt chloride was used to treat the anemia of CKD [145]. Cobalt induces erythropoiesis, acting as an inducer of hypoxia-inducible factor (HIF) [146]. Because of its side effects, including cardiomyopathy and thyroid dysfunction, its use was discontinued [147]. There is a positive correlation between serum cobalt levels and atherosclerosis in MHD patients [112]. More rigorous studies are needed to examine the potential benefits and hazards of cobalt intake for chronic dialysis patients.

Silicon

Silicon has been thought to be an essential element involved in bone mineralization [148]. There is a unique affinity of silicon to aluminum, and it has been suggested that silicon deficiency could be a predisposing factor for aluminum toxicity [149]. Silicon is excreted primarily in the urine, and silicon may accumulate in chronic dialysis patients [150,151]. Silicon is found to accumulate in a normal aging population over 60 years, still higher levels of silicon were detected in the liver, spleen, lungs, skin, bone, and vessels of chronic dialysis patients who are at higher risk of toxicity. In addition, MHD patients develop higher plasma levels than nondialyzed uremic patients [152]. There is a reported association between silicon accumulation and perforating folliculitis [153] and liver and neurologic dysfunction [154,155]. Additional consequences or benefits of silicon deficiency or accumulation have not been well investigated in chronic dialysis patients.

Alterations in nonessential trace elements, metals, and metalloids in patients with kidney disease

Aluminum

Aluminum accumulation was historically described in MHD patients as a consequence of using hemodialysate prepared from tap water that was contaminated with aluminum sulfate added as a purifying agent [156,157]. Aluminum is added to the water in the form of alum to remove suspended colloidal matter by a process called flocculation. Tap water may also be derived from sources such as streams or rivers that may naturally contain higher levels of aluminum. Other potential sources of aluminum include dietary sources, aluminum-containing phosphate binders, and aluminum-containing antacids [158]. In addition, aluminum can be a contaminant or impurity in various other dialysis-associated medications, especially injectable iron, insulin, and EPO [159].

Aluminum accumulates in a variety of organs in chronic dialysis patients, including the lungs, skin, brain, and bone [160–162]. It is present along the mineralizing front of bone. The deposition of aluminum in bone may be underdiagnosed in MHD patients who may be asymptomatic even when a significant amount of aluminum deposition has occurred [163].

Diabetes mellitus and citrate intake are risk factors for increased aluminum accumulation [164,165]. Dietary citrate makes a complex with aluminum, thereby facilitating its intestinal absorption. Citrate also promotes aluminum absorption by enhancing the solubility of this mineral over a wider range of pH values. With respect to these effects of citrate, a careful assessment may be needed with the recent introduction of citrate-based binders, although a RCT did not show a significant difference in serum aluminum levels between the binder-treated group and the nontreated controls [166].

Aluminum accumulation has been shown to cause anemia [167], low-turnover bone disease [168], and dialysis dementia [169]. Studies have also implicated aluminum accumulation with left ventricular hypertrophy [170,171]. With improvements in water treatment, reduction in the use of aluminum-containing phosphate binders, and the not infrequent monitoring of plasma aluminum levels, aluminum-related diseases have largely disappeared in chronic dialysis patients. Of interest, studies have observed tissue aluminum accumulation in patients with nephrogenic systemic fibrosis (NSF) and calciphylaxis [172]. The sources and consequences of aluminum accumulation in these disease processes are unknown. Aluminum toxicity is treated by identifying and removing sources of aluminum, prudent use of deferoxamine chelation and, in high-dose toxicity, treatment with high-flux intensive hemodialysis.

Antimony

Antimony (Sb) is a nonessential metalloid. Sources of antimony exposure include both occupational (welding and smelting) and therapeutic sources [173]. Exposure to antimony can also occur from environmental waste, especially in areas where electronic waste recycling is conducted. Antimony is widely used in its pentavalent form to treat visceral leishmaniasis and as pentamidine to treat pneumocystis infection. Trivalent antimony is known to degrade heme and is a potent inducer of heme oxygenase [174].

Antimony therapy can induce nephrotoxicity, causing both AKI and renal tubular acidosis [173]. No data are available on the blood and tissue antimony levels of patients with CKD.

Arsenic

Arsenic (As) is nephrotoxic, particularly after acute exposure to arsine [175–177]. Patients exposed to arsenic develop hemolysis, acute kidney failure with cortical necrosis, CKD, and peripheral neuropathy [177–179]. The source of arsenic appears to be more diet related in the dialysis population. Arsenic accumulates in MHD patients more than in peritoneal dialysis patients, likely due to the better clearance by CAPD [180].

Arsenic accumulates in the serum and tissues of patients with renal insufficiency [181,182]. A study of human kidney epithelial cells indicates that long-term exposure to arsenic, even at low levels, can increase the risk of kidney fibrosis; this is mediated in part by DNA methylation [183]. This raises the possibility that some of the toxic changes can be reversed by epigenetic therapeutics [183]. Sources of arsenic include contaminated water and food, such as tilapia fish. Cutaneous manifestations of chronic arsenic exposure are generalized hyperpigmentation, palmoplantar hyperkeratosis, and Mees' lines in the nails [184]. Arsenic induces oxidative stress, and chronic arsenic exposure may be a causal factor for atherosclerosis, progression of kidney disease, and increased risk of cancer [185–187].

Cadmium

Cadmium (Cd) levels are increased in the blood and bone of MHD patients [13,47]. Major environmental sources of cadmium include the diet and smoking [188]. Cadmium toxicity has been associated with increased risk of cancers, kidney disease, and osteoporosis [189]. A study from Japan identified cadmium toxicity as causing itai-itai disease with characteristic clinical features, including renal tubular dysfunction, osteomalacia, and anemia with low EPO levels [190]. Animal studies show that the mechanism of anemia development may be through hemolysis, iron deficiency, and changes in iron metabolism with insufficient EPO production [191]. A study from Sri Lanka has suggested a link between environmental cadmium exposure and CKD of unknown etiology [192], although other studies have not confirmed these findings [193]. Preclinical research suggests that cadmium may induce diabetic nephropathy [194], and clinical studies have suggested a pathogenic link between cadmium and worsening diabetic nephropathy [195]. Cadmium is thought to mediate these pathogenic effects by worsening both glycemic control and direct nephrotoxicity. Cadmium may also cause vascular toxicity, since there is a significant and direct association between serum cadmium levels and endothelial dysfunction, as measured by decreased flow-mediated dilatation, in MHD patients [196].

An association has been reported between elevated blood cadmium levels and increased 18-month all-cause mortality in diabetic MHD patients [197]. These findings are consistent with the possibility that cadmium may exert systemic toxicity through its nephrotoxic (tubular toxicity), proinflammatory, and vasculotoxic/proatherosclerotic effects [112,189]. In fact, a study suggests an association between environmental cadmium exposure and malnutrition, inflammation, and protein-energy wasting [malnutrition–inflammation–cachexia (MIA) syndrome] in MHD patients [198,199]. Elevated serum cadmium levels ($>1.38\,\mu g/L$) were associated with a 10-fold increased risk of inflammation [198].

In addition, cadmium exposure has been associated with a higher incidence of hypertension, especially in women who are nonsmokers [200]. It is possible that the cause of the hypertension may be due to an alteration in the tubular expression of cytochrome P450 enzymes that catalyze the hydroxylation of arachidonic acid. This reaction produces eicosanoid 20-hydroxyeicosatetraenoic acid (20-HETE), which is involved in vascular function, and salt excretion by the kidney, and may thereby regulate blood pressure. The 20-HETE can be measured in the urine [199].

Urinary cadmium excretion may be used to assess total body cadmium content. Interpretation of urine cadmium losses needs to be done with caution in elderly, diabetic, or hypertensive patients and in heavy smokers, as in these populations the cadmium excretion can be lower due to nephron loss. Elevated urinary excretion of an *N*-acetyl-β-D-glucosaminidase and β2-microglobulin has been used as an indicator of the toxic effects of cadmium on the kidney. Cadmium toxicity may also inhibit glucose reabsorption and reduce renal zinc reabsorption [201]. Thus it may be important to limit cadmium accumulation in MHD patients by avoiding smoking and restricting the intake of foods with high cadmium concentrations, which include shellfish, particularly Pacific oysters, and mushrooms, such as *Agaricus subrufescens* Peck.

Gadolinium

Contrast agents containing gadolinium are used in MR imaging. Chelated gadolinium is administered as a paramagnetic agent for contrast-enhanced MR imaging. Gadolinium belongs to the lanthanide series of metals, and in its free form, it is highly cytotoxic. To minimize this toxicity, gadolinium is administered in a chelated form with high kinetic stability so that, under normal endogenous conditions, gadolinium dechelation usually would not occur. Most of the administered gadolinium chelate is excreted promptly through the urine, and the half-life ($t_{1/2}$) of gadolinium in patients with normal kidney function is about 60–90 minutes. Gadolinium contrast agents have been implicated in a serious fibrosing disorder known as NSF in patients with advanced kidney insufficiency [202,203]. Based on this evidence, the US Federal Drug Administration issued a black-box warning cautioning against the use of gadolinium contrast agents in patients who have an estimated glomerular filtration rate of less than 30 mL/min. Patients with NSF may develop fibrosis and ectopic calcification/bone formation in the dermis, subcutaneous tissues, heart, diaphragm, testes, and dura mater [202]. Clinically, this is manifested by edema, a plaque-like rash, woody induration of the extremities, tethering of the skin, and severely restricted joint mobility (Fig. 27.1). The pathology is characterized by the infiltration of $CD34^+$ spindle cells and macrophages, angiogenesis, and fibrosis [204]. Patients with kidney insufficiency are susceptible to gadolinium toxicity for a variety of reasons. First, administered gadolinium chelates are retained for prolonged periods in people with advanced CKD. The $t_{1/2}$ for gadolinium can be prolonged for up to 32 hours in MHD patients and up to 20 days in CPD patients. Second, gadolinium contrast agents can induce iron mobilization that may, along with other endogenous metals such as zinc and calcium, induce dechelation of the gadolinium contrast (also known as transmetallation) and lead to tissue deposition of gadolinium phosphate. Among the gadolinium contrast agents, those with a linear structure (such as gadolinium-DTPA-BMA, Omniscan) are less stable than the macrocyclic agents and, thus, are more likely to cause NSF [205–207]. There is high mortality associated with NSF [208]. The use of sodium thiosulfate, rapamycin, and kidney transplantation may all have a role in the treatment of NSF [206,208]. Some studies have shown gadolinium accumulation in the brain of patients with normal kidney function who undergo repeated gadolinium-based contrast exposure. Gadolinium accumulates in cerebellar dentate nucleus and globus pallidus and other gray matter. The clinical significance of this accumulation is currently unknown [207,209].

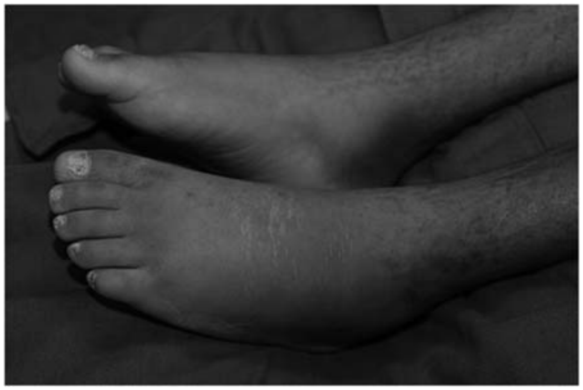

FIGURE 27.1 Gadolinium-induced nephrogenic systemic fibrosis.

Germanium

Germanium is a nonessential trace element. Germanium-containing compounds were formerly used as dietary supplements and endogenous medicines and now are not as commonly used [210]. Germanium trioxide ingestion has been linked to renal tubular toxicity in humans [210–212]. Glomeruli, which may form foamy podocytes, and distal renal tubules, with acute tubular necrosis, are specifically affected. Tissue lipofuscin accumulation and associated neuromuscular weakness are other specific manifestations of germanium toxicity. Recovery of kidney function from germanium toxicity is slow and incomplete [213].

Lanthanum

Lanthanum carbonate is a commercially available intestinal phosphate binder that is prescribed for patients with advanced CKD. Prolonged use of lanthanum-based phosphate binders in animals or humans with advanced CKD has been associated with an increase in serum lanthanum levels and accumulation of lanthanum in the bone [214]. In studies in animals with CKD, orally administered lanthanum has been demonstrated to accumulate in the liver and bone [215,216]. There are reports of GI deposition especially in the upper GI tract [217]. These deposits can be associated with such nonspecific symptoms as dysphagia, nausea, and gastritis; the long-term effects are not known [217].

Lead

Lead toxicity can be acute, subacute, or chronic. Lead exposure and accumulation is a well-known cause of CKD [218,219]. Lead exposure can occur from occupational activities, through the intake of medications or local moonshine preparations, leached from cooking pots, ingestion of paint or other substances, or inhaled from lead-containing fumes, particularly during the time when lead-containing gasoline was used. Lead exposure is declining in the United States due to stringent occupational health oversights [220]. The clinical presentation of acute and subacute lead toxicity can include colicky abdominal pain, arthralgia, fatigue, changes in mental status, and anemia [221,222]. Studies suggest that up to 15% of patients diagnosed with essential hypertension may have a high lead burden [223,224]. Blood lead levels correlate with the risk of CKD in large population studies [225]. Serum and bone lead levels are increased in chronic dialysis patients [226,227] and in CKD patients [228].

Overt lead nephropathy presents as a chronic tubulointerstitial disease accompanied by glucosuria, aminoaciduria, low-molecular-weight proteinuria, hypertension, hyperuricemia, and gout (saturnine gout) [229]. Patients with lead toxicity may present with a neuropathy and may also have significant anemia; the red blood cells may have Howell–Jolly bodies. Lead that accumulates in bone can undergo recycling into the serum during states of increased bone turnover; for example, with hyperparathyroidism, and the mobilized lead may, in turn, cause clinical lead toxicity [230]. Low-level chronic lead exposure has been causally linked to the progression of kidney disease, and ethylene diamine tetra acetic acid (EDTA) chelation has been shown to retard the rate of progression [231].

Mercury

Mercury (Hg) has been implicated in a variety of kidney diseases. Historically, mercury-containing compounds were used to treat syphilis and as diuretics [232,233]. Environmental and occupational exposures also contribute to increased body mercury burden and toxicity [234]. Inhalation of mercury vapors may also cause toxicity, including encephalopathy; for example, the Mad Hatter. Mercury has been implicated as a cause of acute tubular necrosis, glomerulonephritis, and CKD [235].

Human exposure to mercury salts occurs primarily through diet (contaminated fish), occupation, and environment; however, other forms of exposure such as through dental amalgams or the use of certain medicinal products are also known [236]. Upon ingestion, Hg is absorbed by the GI tract and deposited in the target organs, including the kidney. Eventually, mercury enters the renal tubular system and is transported to the intracellular compartment via different transporters, including organic anion transporters; the impact is worse in an already injured kidney and also in the aging kidney. Thus the renal effects of Hg exposure may be worse for people who already have CKD [235,237].

Molybdenum

Molybdenum (Mo) is a constituent of molybdoenzymes that participate in oxidation–reduction reactions. It is also an important cofactor for xanthine oxidase and xanthine dehydrogenase. Molybdenum is known to be increased in the serum and hair of MHD patients [181]. Abnormal molybdenum accumulation may contribute to dialysis-related arthritis [238]. Molybdenum may interfere with normal copper homeostasis and increase urinary copper excretion. Excessive dietary molybdenum intake may result in gout-like symptoms [239]. Other consequences of increased molybdenum levels in patients with kidney insufficiency are currently unknown. Molybdenum-based polyoxometalate nanoclusters may act as antioxidants and improve AKI induced by reactive oxidation species in mice [240].

Nickel

Nickel (Ni) is a well-known environmental and occupational toxin that is prevalent in industries involved with nickel cadmium battery manufacturing and electroplating and electroforming. Nickel is known to be cytotoxic and carcinogenic. These effects of nickel appear to be mediated through multiple mechanisms, including oxidative injury from reactive oxygen species. The mitochondria-mediated apoptotic signaling pathway may also contribute to nickel toxicity [241].

Exposure to nickel could be a risk factor for kidney disease, as indicated by studies of urinary nickel. Urinary nickel levels are positively associated with albuminuria and β2-microglobulinuria [242]. However, a defined role for nickel in human physiology or pathophysiology is lacking. Possible mechanisms of cellular injury may include the inhibition of fibrinolysis, thus promoting fibrosis (mimicking hypoxia), nickel-induced interference in the mitochondrial transport chain, or amplification of reactive oxygen species, which thereby exacerbate oxidative stress [243]. However, there are also data that nickel may cause cellular injury by oxidant-independent mechanisms [244].

Nickel levels are reported to be both lower and higher in patients with renal insufficiency [245]. Dermatitis due to nickel has been reported in MHD patients [246]. Nickel inhibits homocysteine synthetic pathways, and there is a negative correlation between serum nickel levels and serum homocysteine concentrations in MHD patients [247]. Nickel is an HIF mimetic and, therefore, has the potential to induce erythropoiesis [248,249]. Although there is an association between nickel compounds and both erythrocytosis and renal cell cancer in animals, strong evidence of such an associative link in humans is lacking [250,251].

Strontium

Strontium (Sr) exposure can happen through diet (cereals, grains, seafood, and beverages) or the contamination of water or medications. Strontium is mainly absorbed through the GI tract and primarily eliminated through the kidneys [252]. It is mainly located in bone in humans. Since strontium is primarily eliminated by the kidneys, it accumulates in patients with reduced renal function [253]. Strontium accumulates in the serum, bone, and calcified tissues of uremic patients [254–256]. Strontium can interfere with osteoblast function and mineralization [256,257]. In animal models and human studies, the accumulation of strontium has been associated with osteomalacia [256–258].

Vanadium

Vanadium (V) exists in several different states of oxidation and can have a valence of +2 to +5. Dietary sources of vanadium include cereals, mushrooms, spinach, and shellfish. There is evidence that serum vanadium levels are increased in MHD patients [47,259]. Vanadium has an effect on glucose metabolism similar to insulin and may have anabolic effects on muscle. Kidney toxicity due to chronic vanadium exposure has been described in animals, but evidence of such an association in humans is lacking [260]. Within the kidney, vanadium may have an affinity for the renal medulla. The mechanism of vanadium-induced renal injury is thought to be oxidative damage leading to lipid peroxidation, DNA degeneration, and denaturation of proteins which were increased in areas of elevated soil vanadium [261,262]. Vanadium has been an element of interest in studies of CKD of unknown origin that occurs in dry regions of Sri Lanka. The soil concentrations of vanadium in these regions were noted to be high, and the numbers of CKD patients were increased.

Trace element abnormalities in renal-specific syndromes

Fig. 27.2 summarizes the abnormalities in trace elements and metals observed in various kidney-specific syndromes. The clinical and pathological effects of these associations, including proofs of causality, need additional investigation.

Diagnostic and therapeutic approaches

Trace element disturbances should be considered in the differential diagnosis of individual clinical presentations as well as in the setting of epidemics. A high index of suspicion is critical for the diagnosis of trace element deficiencies and toxicities. Measurement of trace elements in serum and tissue samples can be helpful in reaching the correct clinical diagnosis. Serum, urine, and tissue concentrations of trace elements, particularly trace metals, can be measured fairly precisely by analytical methods such as atomic absorption spectroscopy (AAS) or inductively coupled mass spectrometry (ICP-MS). There is a high level of sensitivity with these methods; the measurements give values in parts per billion with AAS and in parts per trillion with ICP-MS. However, these are tissue-destructive techniques, and there is a lack of information concerning the distribution of trace elements within the tissues. To image the distribution of trace metals, several novel methods with high spatial resolution (i.e., the ability to image at submicron levels) in biologic samples are available [263]. These include electron microprobe, laser ablation microscopy-coupled ICP-MS, and synchrotron-based X-ray fluorescence.

Therapeutic approaches to correct trace element and metal deficiencies include dietary supplementation and the use of parenteral replacement as necessary. Toxic accumulation can be treated by removing the sources of toxins. The use of appropriate chelating agents to remove the toxic element must be considered. Successful

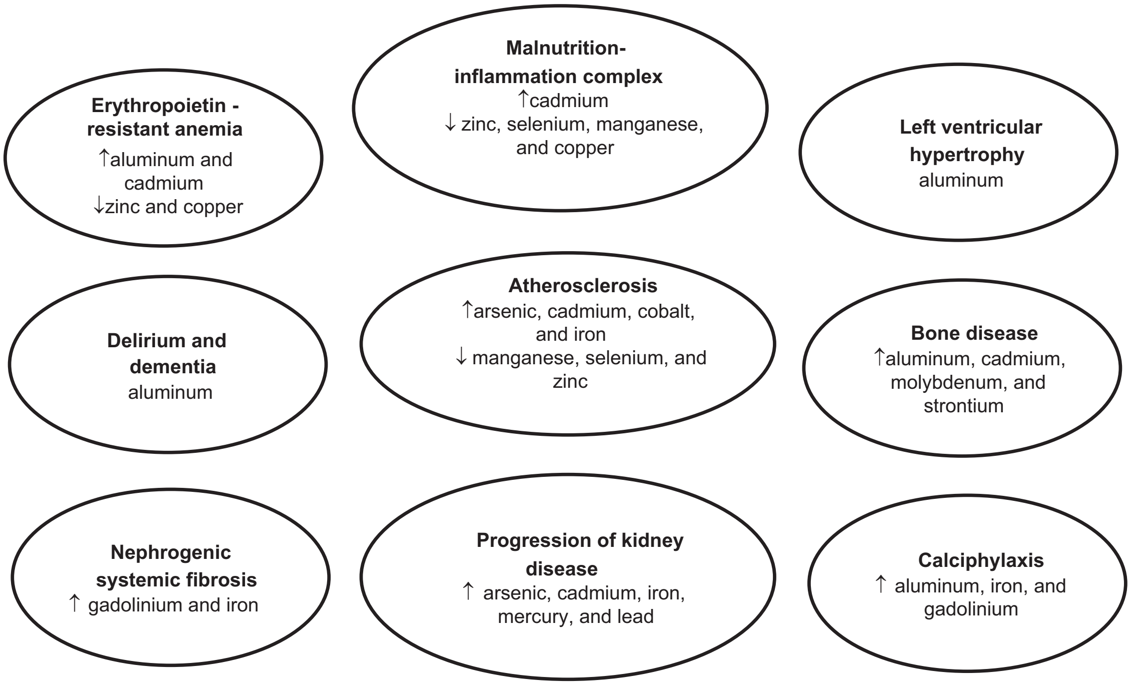
Erythropoietin - resistant anemia
↑aluminum and cadmium
↓zinc and copper
Malnutrition-inflammation complex
↑cadmium
↓ zinc, selenium, manganese, and copper
Left ventricular hypertrophy
aluminum
Delirium and dementia
aluminum
Atherosclerosis
↑arsenic, cadmium, cobalt, and iron
↓ manganese, selenium, and zinc
Bone disease
↑aluminum, cadmium, molybdenum, and strontium
Nephrogenic systemic fibrosis
↑ gadolinium and iron
Progression of kidney disease
↑ arsenic, cadmium, iron, mercury, and lead
Calciphylaxis
↑ aluminum, iron, and gadolinium

FIGURE 27.2 Trace element and trace metal abnormalities in different renal syndromes.

examples of chelation therapies include the use of deferoxamine to treat aluminum toxicity and the treatment of lead accumulation with EDTA chelation. Dialysis therapy, in conjunction with chelation therapy, may be effective for the treatment of some trace element toxicities in patients with advanced CKD or ESRD.

Conclusion

This review summarizes the current knowledge of what is known and not known concerning alterations in trace elements, metals, and metalloids in kidney disease and kidney failure and the syndromes that may be associated with these altered trace element burdens. Of importance to nephrology is the recognition that perturbations in trace element metabolism may contribute to the pathogenesis of AKI (e.g., selenium deficiency) and CKD, including diabetic nephropathy (e.g., cadmium toxicity) and some of the major manifestations of the uremic syndrome such as anemia, EPO resistance, protein-energy wasting, the malnutrition–inflammation syndrome, and atherosclerosis. The intake of trace elements may be compromised due to CKD-driven anorexia superimposed on the dietary restrictions for CKD patients. Trace element losses are compounded by the need for diuretics and the losses that occur from renal replacement therapies. The risk factors for CKD compound the propensity for these derangements. GI absorption and metabolism also change in CKD patients and may lead to further alterations in the accumulation or deficiency of some trace elements.

The previous data support the suggestion that, for advanced CKD and chronic dialysis patients, routine monitoring of trace elements and targeted trace element supplements may be very beneficial. Further studies are needed to determine more exact therapeutic strategies. For people with kidney disease and kidney failure, more studies are also needed to examine the pathophysiological and clinical importance of altered serum concentrations or body burden of different trace elements, to develop more precise methods for assessing trace element burden, and to identify more effective therapies to treat trace element deficiency and excess.

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PART V

Nutritional management of clinical conditions associated with kidney disease

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CHAPTER

28

Nutritional and nonnutritional management of the nephrotic syndrome

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Introduction

The nephrotic syndrome is a consequence of the urinary loss of albumin and other plasma proteins of similar size and is characterized by hypoalbuminemia, hyperlipidemia, and edema formation [1–4]. The change in plasma protein composition has effects on immune function, risk of thrombotic events, and vascular injury. While albumin is the principal protein found in the urine, comprising between 75% and 90% of urinary protein, many other proteins are lost as well. These include immunoglobulins, transferrin, ceruloplasmin, and the binding proteins for vitamin D [5]. Albumin is the principal zinc carrying protein in plasma. Thus iron, zinc, selenium, boron, and copper may be lost in the urine and exhibit decreased plasma concentrations [6–9]. This results in decreased plasma levels of many proteins, including albumin and IgG [10]. The homeostatic response either to reduced plasma oncotic pressure (π) or the loss of specific proteins leads to increased synthesis of proteins that are not lost in the urine, such as fibrinogen, and, thus, an increase in their plasma levels [11–14]. The levels of a variety of lipoproteins are also increased through mixed mechanisms involving a combination of increased synthetic rate and decreased clearance. Urinary losses of erythropoietin [15,16] and iron bound to transferrin [17] may lead to anemia. Other nutrients lost bound to proteins may cause reduction in trace metals or vitamins requiring replacement. Additionally, the net loss of amino acids may result in muscle wasting [18,19]. In addition to alterations in plasma protein composition, both proteinuria and decreased plasma π lead to increased renal sodium retention as well as edema formation [20].

Hyperlipidemia in the nephrotic syndrome is characterized by increased triglyceride levels, increased levels of low-density lipoprotein (LDL) [21], and either a normal or reduced level of high-density lipoprotein (HDL) [22]. The atherogenic lipoprotein(a) [Lp(a)] is also increased as a consequence of an increased synthetic rate [23]. Disordered lipid metabolism imposes at least the potential for increased atherogenic risk to this patient population. Thus the primary manifestations of the nephrotic syndrome are altered plasma protein composition, decreased tissue protein pools, hyperlipidemia, edema formation, and loss of micronutrients and present a variety of therapeutic targets both for dietary intervention and pharmacologic intervention. Some of these are indeed useful, some are not, and some may increase injury.

Albumin homeostasis in the nephrotic syndrome

Albumin is the most abundant protein in plasma. The most notable change in plasma protein composition in the nephrotic syndrome is hypoalbuminemia as a consequence primarily of urinary loss accompanied by an increase in the albumin fractional catabolic rate (FCR) [24]. This stands in contrast to the reduction in FCR that accompanies hypoalbuminemia in protein malnutrition [25,26]. The total albumin pool in a healthy adult is approximately $260\,\mathrm{g}/1.73\,\mathrm{m}^2$

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with approximately 40% of that pool found in the vascular compartment [27]. Although albumin synthetic rate may be increased in the nephrotic syndrome, in some cases to more than twice the average rate [28], it is insufficient to replace the combined losses of albumin due to urinary excretion and increase in FCR. The reason why albumin levels are so sensitive to external loss, despite the rather large basal reserve, is that albumin has a relatively long half-life, approximately 12–20 days. Thus the fraction of albumin synthesized per day that is lost into the urine is quite high. Other proteins of similar size, such as prealbumin (transthyretin), have a more rapid turnover rate, and, thus, the fractional losses are much lower [29]. The basal synthetic rate of albumin is approximately 10–14 g/day; urinary losses in the average range for a nephrotic patient of 5 g/day represent 30% of the total daily synthetic rate. Furthermore, if albumin concentrations were not reduced, the urine losses would be even greater, assuming a constant renal clearance, putting a further challenge on the capacity of the liver to increase albumin synthesis in response to external loss. In experiments that we conducted, when albumin synthesis was increased by dietary protein supplementation, urinary albumin excretion increased as did the absolute and FCR of albumin, presumably representing increased renal catabolism of filtered albumin, while serum albumin concentrations actually decreased [28–30]. The lack of an increase in serum albumin concentrations was not only in part a consequence of increased renal albumin clearance, as well as an increase in the FCR of albumin, but also in part a consequence of the limits of hepatic albumin synthesis.

The mechanism of increased albumin synthetic rate is that of increased gene transcription [13,31]. While the direct stimulus for increasing albumin gene transcription is unclear, it may be linked to plasma π. It is accompanied by increased transcription of other liver-derived proteins, such as transferrin [32], that may be lost in the urine as is albumin. However, gene transcription of other proteins that are not lost in urine because of their large size, such as fibrinogen, may also increase [13,14,32]. The increased gene transcription of these additional proteins is accompanied by increased rates of synthesis that correlate with that of albumin [14]. In the case of fibrinogen, the plasma levels are actually increased as a consequence of this response in synthetic rate [14,33,34]. Synthesis of other proteins, such as apolipoprotein (apo) B [35] and Lp(a) [36], is also increased but does not appear to be correlated with that of albumin and will be discussed with regard to lipoprotein metabolism. Additionally, synthesis of other proteins, such as $\alpha 2$ macroglobulin and $\alpha 1$ inhibitor 3, is also greatly increased [37] but not linked to the rate of albumin gene transcription [37–39].

It should also be recognized that total-body protein synthesis does not increase in the nephrotic syndrome [40]. So the partial replacement of the plasma proteins lost in the urine is essentially enabled by reduced protein synthesis elsewhere, including in skeletal muscle, which may lead to total-body protein wasting.

Dietary protein

The nephrotic syndrome may be compared to the type of protein–energy malnutrition known as kwashiorkor. In both cases plasma volume is expanded, albumin concentration is reduced, and albumin pools shift from the extravascular to the vascular compartment. Metabolic changes in the nephrotic syndrome include the depletion of plasma [28,30,41–44] and tissue protein pools [18,45,46]. However, unlike the nephrotic syndrome, in the case of protein malnutrition it is possible to correct all of the derangements by providing the needed proteins and calories. Although average values for proteinuria in the nephrotic syndrome range from 6 to 8 g/day [28,42,47,48], approximately the amount contained in a hen's egg, it has not been demonstrated that the replacement of protein loss can be achieved only by increasing dietary intake. In fact, dietary protein supplementation causes a greater defect in the filtration barrier of the glomerular capillaries [30,49] resulting in increased urinary protein losses (Fig. 28.1).

Yan et al. in a recent systematic review and meta-analysis, which analyzed 19 trials with 2492 subjects, documented that a low-protein diet reduced the rate of decline in renal functionality and the risk of kidney failure in chronic kidney disease (CKD) patients but did not produce a clear beneficial reduction in all-cause death events [53]. A low-protein diet also reduced the serum phosphorus concentration as well as body mass index. Hence, the nutritional status of CKD patients undergoing dietary protein restriction should strictly be monitored.

Dietary protein supplementation is followed rather promptly by an increase in both renal and splanchnic blood flow, an increase in glomerular filtration rate (GFR) in both humans [54] and experimental models in vivo [40,55–57], and by increased permeability of the glomerular capillary to protein. Consequently, urinary excretion of albumin increases when patients or animals affected by nephrotic syndrome have a high protein intake [28,30,58–60], although a part of increased albuminuria may be a consequence of the increased dietary acid load associated with protein intake, acting through an endothelin-mediated effect [61,62]. Moreover, the increase in albuminuria is not

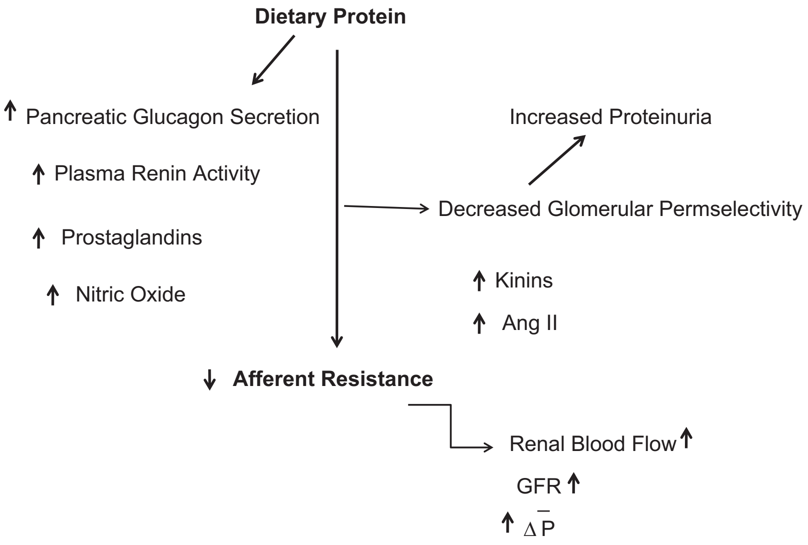

FIGURE 28.1 Dietary protein augmentation causes increased secretion of glucagon by the pancreas, alters activity of the renin–angiotensin axis, increases release of nitric oxide, and augments renal prostaglandin synthesis [50]. These, and possibly other hormones, increase renal blood flow, GFR, and under some circumstances, increase hydraulic pressure across the glomerular capillary. These processes combine to decrease the selectivity of the glomerular capillary and increase proteinuria. Pharmacologic intervention that blocks either kinin, Ang II or aldosterone prevents the increase in proteinuria [45,47,51,52]. *Ang II*, Angiotensin II; *GFR*, glomerular filtration rate.

due to increased plasma albumin levels. Studies have documented that plasma albumin levels either remain the same or decrease following dietary protein augmentation, and the plasma albumin level invariably increases when dietary protein is reduced [30,45,51,63]. Also the fractional rate of albumin catabolism, which is the fraction of the plasma pool catabolized per unit time, increases in nephrotic patients receiving a high-protein diet [28]. It might be more informative to examine the fractional excretion of a specific protein rather than the total excretion, to evaluate the magnitude of the injury to the filtration barrier as well as to provide prognostic information [64,65]. Increase of dietary protein intake has three different effects on albumin: (1) an increase in albumin synthetic rate, (2) an increase in the fractional renal excretion, and (3) an increased fractional rate of albumin catabolism. The second and third ones predominate. It is not clearly understood whether the increased fractional rate of protein catabolism is a direct effect of the dietary protein intake on the albumin catabolic rate in catabolic sites throughout the body, or, instead, whether this is a consequence of increased renal filtration of albumin followed by increased uptake and catabolism in the kidney of a greater amount of filtered albumin that may occur when eating a high-protein diet. However, the increased fractional rate of albumin catabolism, as well as the increased fractional renal clearance, will reduce albumin levels and reduce the positive effect of increased albumin synthesis. Of general metabolic and nutritional concerns, proteinuria is not associated with a change in entire body protein synthesis [19], so the net losses of protein determined by proteinuria result in the loss of tissue protein pools elsewhere.

In this regard, studies have investigated the molecular mechanisms underlying protein reabsorption in the proximal tubule [66]. Megalin, the first receptor that has been studied, binds a variety of filtered molecules and is able to mediate endocytosis in the cytoplasmic tail. Cubulin is a peripheral membrane protein and is dependent on megalin to ensure internalization of its ligands. Independently of megalin, cubulin also interacts on the apical membrane with another protein, known as amnionless. The association between amnionless and cubulin is mediated through the epidermal growth factor–like repeats in cubulin [66]. Urinary albumin excretion can be increased in nephrotic mice by knocking out megalin and cubulin, increasing urinary albumin losses; however, there is no effect on serum albumin levels [67].

In physiological conditions, all filtered proteins are internalized by the receptor complex megalin/cubulin/amnionless, and the proteins are degraded within lysosomes. Normally, low–molecular-weight proteins are filtered, reabsorbed, and catabolized proximally. Even proteins as large as albumin are filtered and reabsorbed, but the fractional clearance is quite low, in the order of 10^{-4}. When glomerular permselectivity is altered, the fractional clearance of larger proteins is increased, and the reabsorptive ability of the proximal tubular cells is overwhelmed. Moreover, proteins, normally completely catabolized by the proximal tubule, such as lysozyme [68], beta-2 microglobulin, *N*-acetyl-beta-D-glucosaminidase, or apo A–I, are found in the urine even though their glomerular clearance is not likely to be increased. Protein accumulation in lysosomes, due to increased protein internalization, is thought to mediate inflammation and fibrosis, eventually leading to renal failure [66].

Thus an increase in dietary protein promotes three independent processes that may modify plasma albumin levels in proteinuric subjects: (1) an increase of albumin synthesis, tending to increase albumin mass; (2) an increase in the fractional rate of albumin catabolism, tending to deplete albumin mass; and (3) an increase in urinary loss, tending to decrease albumin mass. Theoretically, increased dietary protein intake might worsen proteinuria through two possible mechanisms. First, increased dietary protein intake increases glomerular capillary hydraulic pressure, which facilitates greater protein passage across the glomerular capillary wall; second, increased dietary protein intake may alter the permselectivity of the glomerular basement pore structure favoring larger pores. Chan et al. [69] found that increased dietary protein increases glomerular ultrafiltration pressure in nephrotic patients without modifying glomerular permselectivity. This would suggest that glomerular porosity is not influenced by dietary protein, and increased capillary pressure is the culprit for worsening of proteinuria. Meek et al. demonstrated in mice and in humans that a high-protein diet increased glomerular cell death and inflammation, indicating that high-protein diets may exacerbate early indicators of CKD [70]. In this light, dietary protein augmentation might worsen proteinuria by increasing glomerular pressures and by increasing porosity of the glomerular basement membrane in nephrotic patients [28] and animals [30].

The physiologic effects of amino acids on renal hemodynamics depend upon the specific amino acids fed or infused. Infusion of branched chain amino acids fails to increase GFR or renal blood flow in humans [54] or rats [71], while infusion of arginine causes important changes in renal hemodynamics [56], but not necessarily a change in urinary protein excretion. Thus neither an increase in dietary branch chain amino acids [71], nor an increase in dietary arginine or its potential precursors (proline, glutamate, and aspartate) [72], despite its role in nitric oxide synthesis, enhances albuminuria. In contrast, an increase in the dietary content of histidine, phenylalanine, tryptophan, tyrosine, lysine, glycine, alanine, serine, threonine, cysteine, and methionine combined has the same effect on elevating albuminuria as does an increase in the same quantity of dietary nitrogen with intact protein. Arginine supplementation has been shown to increase proteinuria in certain models of proteinuria in the rat [73], while a methionine–threonine-supplemented diet did not. A diet consisting of increased soy protein has been demonstrated to reduce reactive nitrogen species and renal injury in experimental models of the nephrotic syndrome [74]. The renal hemodynamic response to dietary protein may, therefore, depend on the specific amino acids in the proteins, rather than simply the amount of solute, total amino acids, protein, or nitrogen in the diet. A clinical trial exploring the effect of dairy-free gluten-free protein sources in children with the nephrotic syndrome is currently being conducted [75].

Since the increase in GFR and renal blood flow may be prevented by somatostatin administration [57], it has been hypothesized that modifications in renal function induced by protein or amino acid administration may be in part hormonally mediated. An increase in dietary protein intake stimulates secretion of glucagon [55], corticosteroids [76,77], and dopamine [78] and enhances expression of the renin–angiotensin system [49], which may stimulate prostaglandin synthesis [50]. Increased pancreatic glucagon secretion seems to be necessary for the increase in GFR and renal blood flow [55] that follows dietary protein augmentation. Nevertheless, infusion of large amounts of glucagon exerted no effect on urinary albumin excretion [79]. Paller and Hostetter showed that high-protein diets increased the expression of the renin–angiotensin system in animals [49], and it is known that dietary protein augmentation alters glomerular permselectivity in subjects with nephrotic syndrome [58]. This observation was also confirmed in another study [47]. However, there are some nonconclusive data on the effects of a low-protein diet on renin secretion by the kidney. Martinez-Maldonado et al. [80] suggested that renal angiotensin-II activity is increased during dietary protein restriction and contributes to renal vasoconstriction and reduced filtration. This observation has not been confirmed by additional robust data, and most clinical and experimental studies suggest that protein administration increases plasma renin activity [47,49,52]. It is generally accepted that dietary protein intake leads to the activation of the renin–angiotensin system, increased renal blood flow and GFR, and worsening of proteinuria in patients with preexisting proteinuria. Also, the inhibition of the renin–angiotensin system with angiotensin converting enzyme (ACE) inhibitors can blunt or prevent the proteinuric effect of dietary protein in experimental renal diseases [81–83] and in nephrotic patients [47,48].

With regard to the changes in GFR with an amino acid infusion, the plasma levels of insulin, growth hormone, and glucagon all increase in response to the infusion, but only changes in glucagon exhibited a significant temporal relationship with changes in GFR [54]. A potential mediator of arginine-induced renal vasodilation may be NO, since arginine is the substrate for NO production. However, in experimental models, arginine supplementation ameliorated both proteinuria and hyperfiltration in diabetic rats and had no effect on urinary albumin excretion in rats with passive Heymann nephritis [72]. Thus as with the protein–renin interactions outlined earlier, there are conflicting data on the relationship between arginine, its effect on renal hemodynamics, and how this translates into alterations in permselectivity.

Augmentation of dietary protein increases single-nephron GFR (SNGFR) and contributes to the loss of residual renal function. In addition, a rise in dietary protein increases protein filtration which exposes the renal epithelial cells both to potentially injurious proteins, such as complement components [84], as well as protein-bound injurious agents. An example of the latter is the fatty acids bound to albumin; with a rise in protein filtration, there is an increased delivery of free fatty acids to renal tubular epithelial cells which can lead to renal fibrosis [85–87]. Iron transported by transferrin is another example [17]. Urinary losses of both transferrin and erythropoietin can lead to anemia secondary both to iron losses and erythropoietin losses [15,16], and the tubular uptake of iron has been implicated as a cause of tubular fibrosis [88]. Glomerular damage and the concomitant increased glomerular permeability result in a marked increase in protein filtration and initially in augmented proximal tubular reabsorption of protein. Filtered proteins are reabsorbed, carrying iron [88,89], complement components [90], and biologically active lipids [91] into the renal interstitial space causing injury. Furthermore, there is an increase in angiopoietin-like 4 released from podocytes as a consequence of the delivery of fatty acids bound to serum proteins. Consequently, tubular protein overload occurs, leading to tubular cell injury and interstitial fibrosis [92]. This process probably involves the induction of cytokines and such other proinflammatory molecules as monocyte chemoattractant protein-1, osteopontin, and platelet-derived growth factor (PDGF) [93]. The trafficking and deposition of excess filtered protein may be a link between the initial glomerular injury and the subsequent development of tubulointerstitial disease. The resulting tubulointerstitial disease is a better predictor of the GFR and long-term prognosis than is the histologic severity of glomerular damage in almost all chronic progressive glomerular diseases, including IgA nephropathy, membranous nephropathy, membranoproliferative glomerulonephritis, and lupus nephritis [94–96]. Furthermore, diets that are high in protein also generate more acid, inducing the kidney to increase ammoniagenesis. Accelerated rates of renal ammonia production due to the increased dietary acid loads accompanying a high-protein diet may also lead to renal injury, possibly by the activation of complement [96,97]. Higher hydrogen ion concentrations also enhance the generation of endothelin-1 in the kidney, which also promotes progressive renal injury as well as increasing proteinuria [61,62]. The reduction in urinary protein excretion that follows dietary protein restriction potentially can have a salutary effect on progressive renal injury through any or all of these mechanisms. Thus any process that reduces urinary protein losses should be encouraged.

Dietary protein restriction also reduces the synthesis and/or gene expression of several proteins that are thought to play a role in progression of renal injury, such as transforming growth factor-ß (TGF-ß) [98], PDGF [99], and fibrinogen [33]. It is not known whether decreased expression of these genes is a direct result of dietary protein restriction or a consequence of secondary effects of a protein-restricted diet, such as decreased proteinuria with reduced contact of the interstitium to filtered plasma constituents or reduced renal ammoniagenesis (Table 28.1). In nephrotic patients the rate of fibrinogen synthesis is increased in proportion to the increased synthesis of albumin [100], and hyperfibrinogenemia may contribute to increased thrombosis associated with the nephrotic syndrome. Moreover, hyperfibrinogenemia may accelerate the progression of renal disease [101]. It is interesting to note that dietary protein restriction reduces the synthesis of both albumin and fibrinogen in nephrotic patients; however, the serum levels of albumin tend to increase, whereas serum fibrinogen levels decrease. Thus dietary protein restriction appears to have a favorable effect on both albumin and fibrinogen metabolism in nephrotic patients.

Several studies suggest that the composition of dietary protein may be as important as the absolute nitrogen content. In experimental studies in rats, dietary

TABLE 28.1 Adverse effects of proteinuria.

Increased tubular reabsorption of protein	
Increased tubular exposure to filtered components of the complement cascade	Recruitment of macrophages
Increased tubular exposure to reabsorbed iron	Increased TGF-β
Increased tubular exposure to biologically active lipids	Increased PDGF
Increased tubular exposure to filtered growth factors	

PDGF, Platelet-derived growth factor; *TGF-ß*, transforming growth factor-ß.

protein augmentation with a mixture of certain amino acids causes a prompt increase in urinary albumin excretion [75], whereas other amino acids, specifically branched-chain amino acids, arginine, proline, glutamine, glutamate, aspartate, or asparagine, are devoid of an effect on proteinuria [83]. Studies by D'Amico et al. [102] and Walser [103] suggest that dietary protein composition may also be of importance in humans with renal disease. D'Amico et al. found that when patients with the nephrotic syndrome were fed a vegetarian soy diet, urinary protein excretion decreased as did blood lipid levels [102]. The diet was also low in fat (28% of calories) and of low-protein content (0.71 g protein/kg normal body weight). The salutary effects of soy diets in nephrotic patients may be a consequence of the amino composition in these diets, although differences in lipid composition or in protein intake may also explain the apparent benefit of these diets as well. In a subsequent study, fish oil was added to the vegetarian soy diet. The addition of fish oil did not give any additional benefit [104]. Administration of an amino acid/ketoacid–supplemented vegan diet also reduces proteinuria and increases serum albumin levels [105]. Walser et al. showed that supplementing a very low-protein diet (0.3 g/kg per day) with essential amino acids or ketoacids not only reduced proteinuria in patients with the nephrotic syndrome but also maintained or improved GFR. In fact, this regimen may induce a prolonged remission, even if the patients resume ingesting a normal diet. As noted by the investigators, the mechanism for this response is not known [106].

Effects of the nephrotic syndrome on solid tissue proteins

While it is more difficult to quantitate the losses of tissue protein, heavy proteinuria has been strongly associated with sarcopenia [46,107,108]. Rats with Heymann nephritis gain weight at a significantly lower rate than normal rats [45]. While increasing dietary protein from 8.5% casein to 40% causes a significant increase in growth velocity in normal rats, dietary protein augmentation causes significantly less improvement in growth rate in rats with Heymann nephritis. Nephrotic rats fed 40% protein gain weight significantly more slowly than do normal rats fed 8.5% protein [45], even though the difference in protein intake between 8.5% and 40% is many times greater than the urinary protein lost in either nephrotic group. When dietary protein is increased from 8.5% to 40% protein, total carcass (mainly muscle) protein pools are increased in normal rats. In contrast, none of the increase in weight of nephrotic rats fed 40% protein is found in muscle but instead is in viscera, namely, liver and kidney [45]. Most of the increased protein nitrogen consumed when high-protein diets are fed to these animals is excreted in the urine as urea [79,109].

Nephrotic rats have a reduced rate of muscle protein synthesis [18] and an increased rate of hepatic protein synthesis, providing a mechanism for growth impairment in these animals. Total-body protein synthesis is the same in nephrotic and healthy rats [110], yet the nephrotic animals must replace the large amounts of protein lost in the urine, which they do through increased hepatic protein synthesis [18]. Similarly, total-body protein synthesis is the same in humans with the nephrotic syndrome as in controls, despite their urinary losses of protein [19]. Amino acid oxidation is reduced in nephrotic animals in response to the urinary protein losses [110]. It is unknown whether this represents an alteration in muscle metabolism [46,111].

These observations have supported the notion that dietary protein augmentation does not replete protein pools that have been depleted in nephrotic patients or animals; but in addition, high-protein diets are detrimental in that they cause progressive renal injury in a variety of experimental renal diseases in animals [1] and in humans [112–114]. Since a high dietary protein intake is of no benefit in nephrotic patients or animals, a high-protein diet, or completely unrestricted diet with regard to protein intake is not recommended.

The long-term safety of a low-protein diet is uncertain. Using leucine turnover rates as a marker of protein breakdown, Lim et al. [115] noted that nephrotic patients maintained positive nitrogen balance and had lower rates of protein degradation on a modestly restricted protein diet (0.9 g/kg/day) over a period of 35 days. Similarly, Maroni et al. [116] demonstrated that nephrotic patients ingesting 0.8 g/kg/day over a period of 24 days maintained positive nitrogen balance. The principal compensatory response to dietary protein restriction was a decrease in amino acid oxidation. In addition, the investigators noted an inverse correlation between leucine oxidation and the degree of proteinuria, suggesting that proteinuria is a stimulus to conserve essential amino acids. Thus modest protein restriction may be a safe and an effective therapy to reduce proteinuria. However, there are no data on the effects of long-term protein restriction to amounts much less than 0.8 g/kg/day in nephrotic patients. It is, therefore, probably not justifiable to place patients who are heavily proteinuric on diets that contain less than 0.8 g/kg/day except on an experimental basis.

It is still not known whether specific protein sources are clinically superior to others, although fruits and vegetables, and especially soy protein, have been evaluated in both animal [117] and human studies [102,104]. The amino acid composition of the protein may turn out to be as important as the quantity of protein in the diet, but no specific recommendations can be made at this time with regard to the amino acid composition of the diet. However, it is probably not harmful to place patients on a largely vegetarian diet, considering the low fat content and the excellent results reported by D'Amico et al. [102].

Dietary proteins as potential allergens responsible for renal disease

Agents that may be potential causes of the nephrotic syndrome, when it occurs without systemic disease, are largely unknown. In some patients with minimal change disease and the nephrotic syndrome or patients with mesangial proliferation, exposure to specific dietary proteins, such as cow's milk, has been implicated as a cause [13–17,105]. Bovine serum albumin and casein have also been identified as an allergen in a patient with immune complex glomerulonephritis. Clinical remission followed the removal of the offending agent from the diet.

Abdel-Hafez et al., in a review article, showed that although some cases of idiopathic nephrotic syndrome may be related to allergies, clear data that it is a type of allergic disorder or that it is caused by a specific allergen are lacking [118]. The authors in this review commented that the proteinuria and high IgE levels in patients with idiopathic nephrotic syndrome are determined by greater interleukin 13 (IL-13) levels. Studies also indicate that IL-13, identified as stimulator of IgE response, may mediate urinary protein losses in patients with minimal change disease due to its ability to induce CD80 expression on the podocyte [118].

There is an association of gluten enteropathy with IgA deposition in the glomeruli and the development of IgA nephropathy, and this may be due to an allergic reaction to gluten in the diet [106]. Overall, it is unclear what fraction of patients with the nephrotic syndrome have food allergy as a causative factor. Nevertheless, the possibility that food allergy might be responsible for the development of specific renal diseases is rarely considered by most clinicians and may be of overlooked importance. More recently, a case–control study did not conclusively confirm a clinically significant role for celiac disease or immune reactivity to gluten in IgA nephropathy [119].

Effects of lipids on renal disease and nephrotic syndrome

Increased dietary lipid intake is associated with increased lipid levels, both of triglycerides and LDL, and higher levels of inflammatory cytokines in experimental models of the nephrotic syndrome compared to animals fed a high protein, low-fat diet [120]. High-lipid diets are also associated with an increased risk of glomerulosclerosis in experimental animal models [121]. Subjecting rats with adriamycin-induced nephrotic syndrome to a higher lipid diet increases urinary protein excretion and exacerbates mesangial proliferation [121,122], suggesting that hyperlipidemia, in addition to being caused by the nephrotic syndrome, contributes to renal injury. Simvastatin treatment was also found to reduce glomerulosclerosis in the same rat model of renal injury [123]. A high-fat diet leads to renal tubular lipid deposition through the activation of the sterol regulatory element binding protein-1 and TGF-β1 [124].

It is generally accepted that both qualitative and quantitative alterations in blood lipids cause macrovascular disease, and hyperlipidemia caused by the nephrotic syndrome is no less dangerous than hyperlipidemia due to other causes. In the process of atherogenesis, lipid-laden macrophages accumulate in the vessel wall, followed by intimal hyperplasia, and ultimately by atherosclerosis. Recent works from several laboratories [125–127] suggest that similar changes may occur in the microvasculature of the kidney, specifically the glomerular mesangium. As detailed earlier, increasing dietary lipids in experimental models of the nephrotic syndrome leads both to increased glomerular injury and lipid accumulation in tubular endothelial cells [120,121]. Delivery of free fatty acids by filtered albumin increases podocyte injury [128]. Al-Shebeb et al. [126] found that focal glomerular sclerosis occurred in guinea pigs fed a high-cholesterol diet for 70 days. The animals developed proteinuria and hematuria. A high-cholesterol diet also caused albuminuria, accelerated focal glomerulosclerosis, and increased glomerular capillary pressure in rats [125].

The obese Zucker rat develops spontaneous hyperlipidemia, proteinuria, and progressive glomerulosclerosis. These processes can be attenuated by cholesterol-lowering drugs [125,129]. It is interesting to note that glomerular capillary pressure and SNGFR are within the normal range, suggesting that hyperfiltration does not mediate the glomerular injury caused by hyperlipidemia [125]. Diamond et al. [127] found that rats with the nephrotic syndrome induced by puromycin aminonucleoside (PAN) had more proteinuria and a lower GFR when fed a high-cholesterol diet as compared to nephrotic rats eating a regular diet. The glomeruli in rats fed a high-cholesterol diet were more sclerotic and had mesangial cell proliferation and foam cells. Lowering plasma cholesterol by the administration of cholestyramine resin attenuated both acute and chronic proteinuria in these animals [125]. It has been hypothesized that increased blood lipid levels, either from dietary cholesterol or from hyperlipidemia caused by the renal disease, may play an important role in intensifying the rate at which established renal diseases progress [125,130] and may even initiate glomerular injury [126,131]. These changes could be due to either hemodynamic changes or the direct injury that follows the uptake of lipids by the glomerulus.

The oxidation of circulating lipids may play a role in progressive renal injury. Glomerular macrophages endocytose LDL both through specific LDL receptors and through the nonspecific scavenger system. It is known that hyperlipidemia activates mesangial cells (which have LDL receptors). This leads to the stimulation of mesangial cell proliferation and to increased production of macrophage chemotactic factors, fibronectin (a component of the extracellular matrix), and reactive oxygen species [132–134]. Both increased mesangial lipid deposition and enhanced expression of LDL receptors on mesangial and epithelial cells have been demonstrated in patients with chronic glomerular diseases. Unregulated absorption of oxidized LDL may then lead to an uncontrolled increase in intracellular cholesterol [135], because oxidized lipids bypass the protective mechanism that regulates LDL uptake. After endocytosis, cholesterol is esterified by acetyl CoA cholesterol acyltransferase to form the insoluble cholesterol oleate ester [135]. This process results in creation of foam cells in the glomerulus analogous to that of early atherosclerosis in blood vessels. Thus the oxidative state of lipids may also play a role in their nephrotoxicity; hence, antioxidant drugs might prove protective.

These studies on animals are supported in part by further, albeit uncontrolled, observations in patients in which reducing lipid levels with an HMG CoA reductase inhibitor reduces proteinuria or slows the rate of progressive injury [136]. Hypercholesterolemia is also a separate independent risk factor for the progression of renal injury in diabetic patients [137].

Lipids represent a wide variety of substances, including steroids, saturated and unsaturated fatty acids, phospholipids, and other compounds, many of which have either direct biological activity or are precursors of important biologically active metabolites. Much attention has been focused on the effect of polyunsaturated fatty acids (PUFAs) on renal hemodynamics and on the manifestations of renal injury.

Disordered lipoprotein metabolism in the nephrotic syndrome

Lipoprotein metabolism is disturbed, in part, as a consequence of both hypoalbuminemia with resulting decreased plasma oncotic pressure (π) and independently as a consequence of urinary protein loss [138]. Of these two related processes, urinary protein losses predominate in the causal pathway. Low plasma π increases hepatic synthesis of apo A–I, apo B, and apo E, while decreased clearance of triglyceride-rich lipoproteins is predominately a consequence of proteinuria [139]. Albumin, and perhaps other proteins as well, increases the delivery of free fatty acids bound to filtered proteins to podocytes, which leads to the release of angiopoietin-like 4, a strong inhibitor of lipoprotein lipase (LPL) [13,140–142]. This results in increased plasma triglyceride–rich lipoproteins as a consequence of inhibition of LPL, which greatly prolongs the half-life of triglyceride-rich lipoproteins. Plasma LDL levels are also increased as a consequence of increased synthesis of apo B [35] as well as reduced LDL clearance due to an increase in proprotein convertase subtilisin/kexin type 9 (PCSK9) levels [143]. Both secretion and hepatic transcription of LDL are increased in the nephrotic syndrome in rat models [12].

The effect of altered glomerular permselectivity on lipid metabolism

The primary drivers of increased lipid levels in the nephrotic syndrome are decreased clearance of triglyceride rich lipoproteins (VLDL, chylomicron remnants) as a consequence of decreased LPL activity and both increased synthesis and decreased clearance of LDL. LPL is primarily decreased as a consequence of the release of angiopoietin-like 4 protein from podocytes due to enhanced exposure to free fatty acids as a result of the increased filtration of albumin [144]. An identical defect in VLDL clearance is observed following the onset of proteinuria in rats with hereditary analbuminemia and in otherwise normal rats following the onset of proteinuria. These findings demonstrate that renal loss of protein rather than renal loss of albumin is the trigger for this hyperlipidemia. Indeed, if increased fatty acid delivery to podocytes is the mechanism for increased plasma lipid levels, fatty acids bound to albumin is not the only pathway leading to this response [139]. Plasma LDL is increased both as a consequence of increased synthesis [35,145] and decreased clearance. Reduced LDL clearance is linked to increased release of PCSK9 by the liver [12,143]. Increases in albumin gene expression parallel the increased gene transcription of such other proteins as transferrin, fibrinogen, and apo A1 [13]. It is unclear whether an increased production of PCSK9 is affected by a similar mechanism, but clearly increased hepatic release of this protein plays a role in reduced LDL clearance and increases in plasma LDL levels.

As mentioned earlier, hyperlipidemia is found in rats with hereditary analbuminemia [138,146,147].

These animals have a reduced plasma π and only trace amounts of albumin in their plasma. The genetic disorder is a seven nucleotide deletion isolated to the MN intron of the albumin gene creating a splicing defect during albumin mRNA processing [148]. Although this finding would suggest that reduced plasma π or reduced plasma albumin concentration alone is the signal to induce the lipid abnormalities described earlier, the catabolism of both VLDL and chylomicrons is normal in these animals [138]. A severe defect in catabolism of both of these lipoproteins follows the onset of proteinuria [149] suggesting that proteinuria plays a role in the pathogenesis of disordered lipid metabolism independent of the serum albumin levels or π. Supporting this hypothesis is the observation that reducing albuminuria by administering ACE inhibitors or dietary protein restriction reduces blood lipid levels [138,149,150] even if neither plasma albumin concentration nor plasma π is increased.

Cardiovascular effects of hyperlipidemia in the nephrotic syndrome

Accelerated atherosclerosis occurs in patients with proteinuria and hyperlipidemia and is probably responsible for the sharply increased incidence of cardiovascular disease and stroke in the nephrotic syndrome [151,152]. Hyperlipidemia is also thought to worsen glomerulosclerosis and enhance progression of glomerular disease [153]. One study reported an 85-fold increase in the incidence of ischemic heart disease in patients with nephrotic syndrome [154]. This is not surprising when one considers that serum HDL, and specifically the HDL_2 fraction, is reduced [22,155] while serum LDL, intermediate-density lipoprotein, and VLDL fractions are high. It is not yet known what the biological significance is of the increased serum Lp(a) levels in the nephrotic syndrome. Lp(a) is a powerful atherosclerotic risk factor when it occurs genetically [156]. However, these high Lp(a) concentrations occur in combination with the low-molecular-weight isoform. Thus it is difficult to know whether it is the increased concentration or the specific type of isoform of Lp(a) that promotes atherogenesis. Some studies suggest that the low-molecular-weight isoform per se may confer the increased atherosclerotic risk [157]. It remains to be determined whether the elevated serum levels of Lp(a) in nephrotic patients also contribute to the increased rate of atherosclerosis observed in this population. While the plasma concentrations of most intermediate-sized proteins are reduced, the serum concentrations of many larger proteins, such as fibrinogen and prothrombin [34], are increased and potentially may play a role in the hypercoagulable state associated with this syndrome [158] and contribute to atherosclerosis. Hyperlipidemia, therefore, is a serious consequence of proteinuria and should be addressed to protect patients from atherosclerosis. Hyperlipidemia may also contribute to the progression of the renal disease [125,130] and may even initiate renal injury [126,131].

Thromboembolic complications

Dyslipidemia can result in acceleration of atherosclerosis as well as increased risk of myocardial infarction or stroke. Moreover, dyslipidemia during nephrotic syndrome may have a causative role in the increased risk of thrombosis associated with this syndrome. Dyslipidemia is one of the more relevant risk factors associated with atherothrombotic disorders [159]. Diuretic use and intravascular volume reduction, protein C and protein S deficiencies, and antiphospholipid antibodies are relevant contributing factors to thromboembolic complications [160]. The deep veins of the lower limb are the most common sites of thrombosis in adults affected by nephrotic syndrome. Renal vein thrombosis is less common, but pulmonary embolism can occur and is most likely to be due to deep venous thrombosis. A retrospective study analyzing diagnostic codes of patients at the time of their hospital discharge showed that deep vein thrombosis occurred in 1.5% and renal vein thrombosis in 0.5% of patients affected by nephrotic syndrome [161].

Another large retrospective cohort study assessed the risk of venous and arterial thromboembolism in patients with nephrotic syndrome. There was a high risk of asymptomatic venous thromboembolism and arterial thromboembolism during the first 6 months of presentation of the nephrotic syndrome. The ratio of proteinuria to serum albumin levels predicted venous thromboembolism, whereas estimated GFR and the traditional risk factors for atherosclerosis were associated with arterial thromboembolism [162]. Currently, there are no randomized control trials that have examined the clinical indications for prophylactic anticoagulant therapy or for how long such therapy should be given. General factors such as the presence of edema, immobility, and a previous history of thromboembolic events are commonly considered when deciding whether to initiate anticoagulant therapy.

The role of polyunsaturated fatty acids

Prostaglandins and thromboxane are metabolic products of PUFAs. They include both vasoconstrictors, such as thromboxane A_2 (TXA_2), and vasodilators, such as PGE_2 or PGI_2, and they may exert important hemodynamic effects. The effects of oxidized lipoproteins may also be mediated by these autocoids [163].

Eicosanoids are derived from PUFA present in the diet, because PUFA cannot be synthesized by mammals. Thus eicosanoid metabolism can be manipulated nutritionally [164]. Lipids derived from marine sources are rich in omega-3 PUFA (e.g., eicosapentaenoic acid), while those derived from vegetable oils are enriched with omega-6 PUFA (e.g., arachidonic acid). Eicosapentaenoic acid competes with arachidonic acid as a substrate for cyclooxygenase and lipoxygenase. Cyclooxygenase converts arachidonic acid to the diene metabolites (e.g., PGI_2 and TXA_2) and eicosapentaenoic acid to triene metabolites (e.g., PGI_3 and TXA_3), respectively [165,166]. Lipoxygenase converts arachidonic and eicosapentaenoic acids to the four and five series of leukotrienes, respectively [167,168]. TXA_2, an arachidonic acid metabolite, is a potent vasoconstrictor, whereas TXA_3, a metabolite of eicosapentaenoic acid, is biologically inert [169]. In contrast, the vasodilators PGI_2 and PGI_3 are equipotent [165].

Changes in the generation of vasodilatory prostaglandins (PGE_2, PGI_2) and vasoconstricting cyclooxygenase metabolites (TXA_2) can occur during renal injury or during physiologic stress, such as plasma volume contraction. While changes in eicosanoid metabolism can contribute to the GFR adaption to renal injury or plasma volume contraction, they may also play a pathogenic role. Because of the differences in biological activity of their vasoconstrictive and vasodilatory metabolites, substitution of eicosapentaenoic acid for arachidonic acid in the diet may alter the expression of renal injury.

The metabolic effects of dietary PUFA, particularly fish oil, have been studied in a variety of experimental models of renal disease, including the nephrotic syndrome [170–172]. In adriamycin-induced nephrosis in the rat, Ito et al. [173] found that plasma cholesterol, triglycerides, creatinine, and proteinuria were significantly lower in rats fed fish oil than in rats fed beef tallow. Glomerular hyalinosis and endothelial swelling were also less in the fish oil–fed rats and were correlated with the changes in plasma triglycerides and cholesterol.

In a subsequent study of the same model, dietary fish oil induced a dose-dependent reduction in glomerular synthesis of dienoic eicosanoids, PGE_2, 6-keto-$PGF_1\alpha$ (a stable metabolite of PGI_2) and TXB_2, a stable product of TXA_2. Fish oil also decreased the generation of TXB_2 from platelets. In studies of rats with nephrotic syndrome induced by adriamycin, Barcelli et al. [174] reported that dietary fish oil (a source of omega-3 PUFA), evening primrose oil (a source of omega-6 PUFA), or a mixture of these two PUFAs reduced plasma triglyceride and cholesterol levels as compared to rats fed beef tallow. The fatty acid composition of the kidney was different in each dietary group, but neither the magnitude of proteinuria nor changes in plasma creatinine were affected by dietary fish oil. In another model of progressive renal injury in the rat, partial renal ablation, Scharschmidt et al. found that diets supplemented with fish oil accelerated the course of renal injury [171] and caused increased mortality.

In studies involving human subjects, Gentile et al. [104] added 5 g of fish oil per day to the diet of patients with the nephrotic syndrome who had been maintained on a soy vegetarian diet. These investigators found no beneficial effect of the fish oil on either proteinuria or on blood lipids when compared to patients maintained on the soy diet without fish oil supplementation. In contrast, Hall et al. [175] found that 15 g of fish oil per day caused a decrease in plasma total triglycerides and in LDL triglycerides and an increase in plasma LDL cholesterol. Donadio et al. [176] treated 55 patients with IgA nephropathy and proteinuria with 12 g of fish oil per day in a prospective, randomized, placebo-controlled study. They found a significant reduction in the rate of progression of renal disease using a 50% increase in serum creatinine concentration as a study end point. However, there was no significant effect on proteinuria or blood pressure. These studies suggest that while alterations in dietary PUFA may alter some manifestations of the nephrotic state, the effects are dependent upon the model being investigated; and the possible therapeutic value of PUFA should still be viewed with caution. The effects of these PUFA supplements may be neither predictable nor salutary for all patients with renal disease.

Harris et al. [177] reported that a diet entirely devoid of essential fatty acids provided renal protection by inhibiting macrophage function. While vasoactive lipids probably do play a role in altering the course of a variety of renal diseases, the effects of specific alterations in the composition and amounts of dietary PUFAs on the course of renal diseases in humans are not completely known. Thus there is no strong evidentiary basis at this time to recommend dietary PUFA supplements to patients with the nephrotic syndrome, with the possible exception of heavily proteinuric patients with IgA nephropathy [178]. Even here the value of using fish oil remains questionable. Recently, it has been shown that there is a lack of knowledge on the role of the fatty acid profile on the course of disease, independent of supplementation, and the type of renal disease, including the nephrotic syndrome [179]. In fact, the majority of studies analyzed the response to PUFA supplementation without considering the impact of the basal fatty acid metabolism on the effects of supplementation.

Derangements in divalent cation metabolism in the nephrotic syndrome

The nephrotic syndrome is characterized by the urinary losses of a variety of proteins in addition to albumin. These losses are potentially accompanied by excretion of metabolites normally bound to the protein. Transferrin is a glycoprotein bound to iron. The loss of iron in the urine provides the potential both for developing iron deficiency and the toxic presentation of iron to renal tubular cells where its uptake may contribute to renal fibrosis [89] [see Chapter 8: Catalytic (Labile) Iron in Kidney Disease]. Urinary transferrin loss is accompanied by an increase in the rate of transferrin synthesis [180] and gene expression [13,32], both of which are correlated with either the rate of albumin synthesis or with gene transcription for albumin rather than with serum iron or markers of inflammation. This suggests that the regulation of the transferrin gene in the nephrotic syndrome is driven in response to plasma oncotic pressure rather than as a homeostatic response to iron losses. Increased synthesis of transferrin is accompanied by increased transferrin losses, thereby exacerbating iron loss [180]. Anemia may also be a consequence of the urinary loss of another glycoprotein that is of a size likely to pass the glomerular filtration barrier in the nephrotic syndrome, erythropoietin [15,181,182]. Indeed, plasma levels of this protein are reduced in both nephrotic patients [181] and rats [15], and it does not appear that synthesis of erythropoietin is increased in response to its urinary loss [15]. There are no prospective randomized studies of the effect of administration of either iron (potentially harmful) or erythropoietin (expensive and inconvenient) to anemic patients with the nephrotic syndrome to guide clinical practice.

While the treatment of iron deficiency is necessary, the primary target for therapy must be the reduction of urinary protein loss. The treatment of anemia may require both iron supplementation and administration of erythropoietic stimulating agents. However, anemia is not the only adverse effect of urinary iron loss. Increased filtration of iron is accompanied by increased tubular reabsorption, which can lead to fibrosis [183–185]. Thus administration of iron to correct iron deficiency mediated by urinary transferrin loss in the nephrotic syndrome may not be without risk [see Chapter 8: Catalytic (Labile) Iron in Kidney Disease].

In addition to iron deficiency, urinary copper losses resulting from the loss of the copper-binding protein, ceruloplasmin, can lead to a significant depletion of this trace metal [186]. Zinc is bound to albumin, and the levels of this divalent cation are found to be reduced in subjects with the nephrotic syndrome, even when consuming high-zinc diets [187]. Loss of zinc has been associated with skin lesions [188], but this complication is uncommon [187]. It is also unclear what role urinary zinc losses play in generating zinc depletion and what contribution is provided by alterations in gut zinc absorption [189]. In contrast to zinc, urinary copper losses, resulting at least in part from increased urinary ceruloplasmin excretion, are associated with both anemia and leukopenia [9,190,191]. Documented zinc deficiency is probably a consequence of reduced intestinal absorption of zinc in conjunction with excessive urinary loss [192]. The effect of proteinuria on zinc metabolism has been largely ignored, and it is not known to what extent zinc depletion plays a role in the clinical manifestations of the nephrotic syndrome.

Hypocalcemia is well recognized in nephrotic patients [193–196] and includes reduced serum vitamin D levels, specifically 25-hydroxyvitamin D and serum ionized as well as total calcium. Hypocalcemia does not result entirely from low serum albumin levels and a reduction in the amount of calcium-bound albumin, since plasma vitamin D is reduced [5,192,193,197]. The decrease in serum calcium concentration correlates with urinary albumin excretion [192]. Plasma albumin and vitamin D concentrations correlate closely. Vitamin D–binding protein is present in the urine of nephrotic patients [5,197], although plasma levels are not decreased. Serum vitamin D levels normalize when proteinuria resolves [193,197]. Labeled vitamin D appears rapidly in the urine of nephrotic subjects [194], suggesting that urinary vitamin D loss is the cause of hypovitaminosis D in these patients. Hypovitaminosis D is not primarily the result of loss of renal mass, since plasma vitamin D levels are also low in nephrotic patients with normal renal function [193–195]. The hypovitaminosis D of the nephrotic syndrome may result in rickets, especially in children [194,196]. Nephrotic patients malabsorb calcium [175], a defect that can be corrected by exogenously administered vitamin D [194]. It is not known whether synthesis of vitamin D–binding protein is altered in response to its urinary loss or whether it is modulated by dietary protein intake. Unlike many of the other manifestations of the nephrotic syndrome, hypovitaminosis D can be managed with replacement therapy.

Derangements in salt and water metabolism in the nephrotic syndrome (volume homeostasis)

One of the defining features of the nephrotic syndrome is edema formation. This is the result of two separate processes, either of which may be dominant. The decrease in plasma oncotic pressure resulting from the loss of albumin and other proteins of similar size would favor edema formation, since it would tend to result in a loss of the difference in oncotic pressure ($\Delta\pi$) between plasma and interstitial space, favoring the flux of fluid from the plasma compartment into the extravascular space (Fig. 28.2). However, the loss of albumin from the plasma compartment is accompanied by transfer of albumin from the extravascular pool into plasma via increased lymphatic return [198] providing a physiologic response that partially balances the decrease in plasma π. Indeed, in health, approximately 60% of the total-body albumin pool is extravascular [30,199], and the extravascular pool is more significantly depleted of its albumin mass than is the plasma pool as a consequence of increased lymphatic return of extravascular fluid [198,200]. This reduces the effect of reduction in plasma albumin concentration with regard to the difference between plasma and interstitial oncotic pressure ($\Delta\pi$). If the entire basis for edema formation was a decrease in $\Delta\pi$ that was great enough to increase the flux of fluid from the vascular compartment into the interstitium to such a rate that it could not be compensated for by increasing lymphatic return, one would anticipate that nephrotic patients would have elements of plasma volume depletion, with increased plasma renin activity, aldosterone, and norepinephrine. While this is found in some subjects, especially among children with some forms of the nephrotic syndrome, it is more the exception.

The second mechanism for edema formation is that of primary renal sodium retention as a consequence of activation of the sodium channel in the collecting duct (ENaC) which can result in plasma volume expansion (Fig. 28.3).

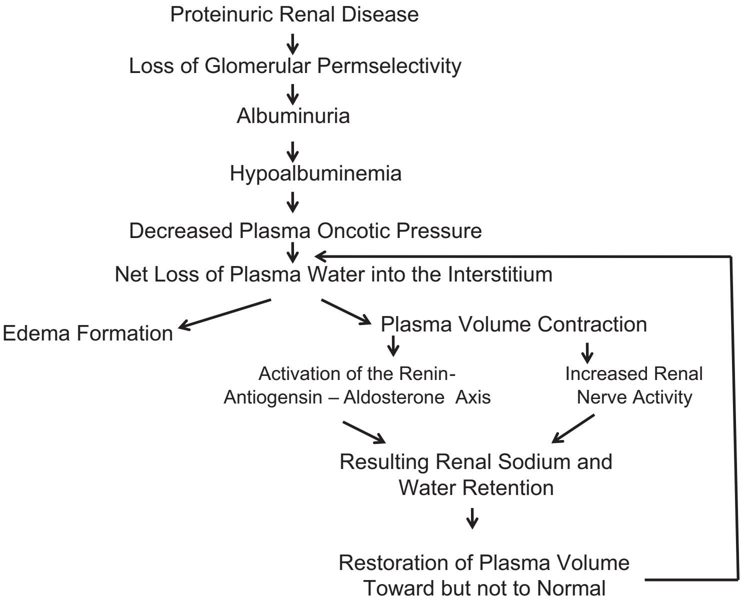
Proteinuric Renal Disease
Loss of Glomerular Permselectivity
Albuminuria
Hypoalbuminemia
Decreased Plasma Oncotic Pressure
Net Loss of Plasma Water into the Interstitium
Edema Formation
Plasma Volume Contraction
Activation of the Renin-Antiogensin – Aldosterone Axis
Increased Renal Nerve Activity
Resulting Renal Sodium and Water Retention
Restoration of Plasma Volume Toward but not to Normal

FIGURE 28.2 Primary edema formation with renal sodium retention. The plasma underfill hypothesis: hypoalbuminemia leads to increased transudation of fluid into the interstitium resulting in plasma volume contraction with secondary activation of the renin–angiotensin–aldosterone axis and subsequent renal sodium retention. Because a normal plasma volume cannot be maintained in the presence of hypoalbuminemia, a positive feedback cycle occurs. The reabsorbed salt and water also enter the interstitial space. Edema formation is a direct consequence of hypoalbuminemia, and salt and water retention is a consequence of the plasma volume contraction that results.

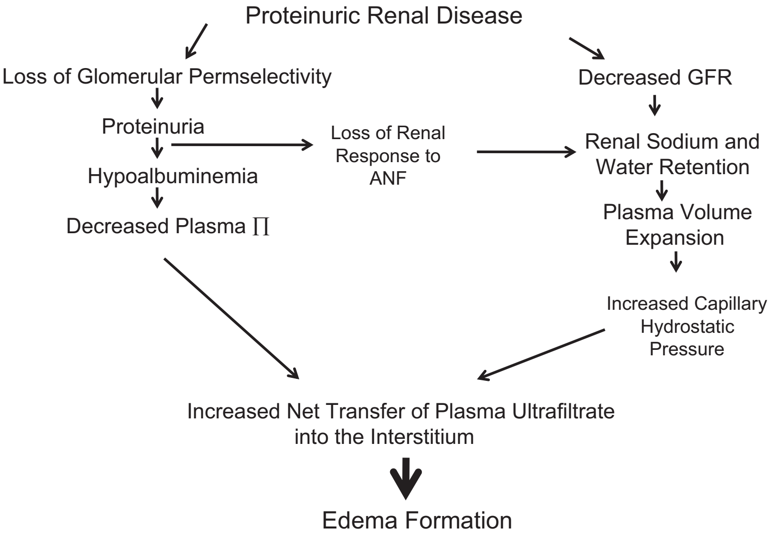
Proteinuric Renal Disease
Loss of Glomerular Permselectivity
Decreased GFR
Proteinuria
Loss of Renal Response to ANF
Renal Sodium and Water Retention
Hypoalbuminemia
Decreased Plasma ∏
Plasma Volume Expansion
Increased Capillary Hydrostatic Pressure
Increased Net Transfer of Plasma Ultrafiltrate into the Interstitium
Edema Formation

FIGURE 28.3 Primary renal sodium retention with edema formation. The plasma overfill hypothesis: renal salt and water retention occurs as a result of the renal disease or protein losses causing plasma volume expansion. This produces increased capillary hydrostatic pressure, which in conjunction with the increased transcapillary flux of fluid resulting from hypoalbuminemia, causes edema. Edema formation is not a direct consequence of reduced oncotic pressure alone. Renal salt and water retention is also a consequence of an unresponsiveness of the kidney to ANP. *ANP*, Atrial natriuretic peptide.

This is a consequence of proteinuria, with an increased presentation of plasma proteases, such as plasmin, as a consequence of filtration of nonalbumin biologically active proteins. ENaC is composed of three subunits: the alpha, beta, and gamma. Plasmin and aprotinin, and presumably other proteases, activate ENaC, by cleaving the alpha and gamma subunits. This offers the potential for the treatment of nonphysiologic Na reabsorption by protease inhibition.

The initial experiment that clearly demonstrated the dominant effect of proteinuria was conducted by Ichikawa et al. in an experiment where proteinuria was induced in one kidney using a puromycin model [201]. The proteinuric kidney retained salt in contrast to the nonproteinuric kidney exposed to the same plasma albumin concentration. In a second study reported by Perico et al. [202] using a unilateral model of proteinuria induced by adriamycin infusion affecting only one kidney, the proteinuric kidney had no natriuretic response to infused atrial natriuretic peptide (ANP). Additionally, plasma volume was expanded in nephrotic animals compared to controls; ANP was elevated, but the animals were still in positive sodium balance. This physiologic pattern is also observed in patients with the nephrotic syndrome [203]. Additionally, exogenous ANP administration to nephrotic patients increased urinary protein excretion leading to a positive feedback loop, where decreased responsiveness of the nephrotic nephron to ANP leads to further volume expansion with resulting increased stimulus for the secretion of ANP.

We reported that the formation of edema, measured as the volume of distribution of ^{22}Na, did not increase in the absence of plasma volume expansion using a model of membranous nephropathy with anti-FX1A serum [204,205]. This model is supported by the observation that albumin infusion to normalize oncotic pressure does not result in a natriuresis [206]. Edema is, thus, a consequence of a reduction in $\Delta\pi$ resulting in an increase in flux of fluid into the extravascular space and an increase in hydraulic pressure resulting from primary renal sodium retention. The increased fluid flux is initially counteracted by increased lymphatic return, bringing with it albumin and other proteins from the interstitial space back into the plasma compartment. This leads to the redistribution of albumin. This model of overfill edema formation would favor treatment with amiloride and/or furosemide or other loop diuretics.

A subset of patients, especially children with the nephrotic syndrome, does not fit into the model of overflow edema and clearly has evidence of hypovolemia consistent with the classic underfill model [207] in which some patients have physiologic evidence of volume depletion, such as increased plasma levels of aldosterone, renin, and norepinephrine as well as increased hematocrit and low urinary fractional excretion of Na. Clearly this does not exclude the possibility of a combined effect of reduced oncotic pressure acting in addition to an inability of the kidney to excrete Na even if plasma volume expansion was induced. Even in patients with minimal change disease and the nephrotic syndrome, plasma and blood volumes are found to decrease when they enter remission [3], suggesting that primary renal sodium retention in these cases is the dominant mechanism (Fig. 28.3).

Additionally, there is evidence, at least in some models, that capillary permeability is increased, adding an additional mechanism to reduction in $\Delta\pi$ and plasma volume expansion [208]. Circulating vascular permeability factors have been identified in lymphocytes or plasma from patients with some forms of the nephrotic syndrome, adding a third potential pathway responsible for the development of edema [209–212]. The treatment of edema should be targeted after some evaluation regarding the dominant mechanism responsible for edema formation in an individual patient.

Ultimately, edema occurs when the amount of fluid filtered into the interstitium exceeds maximal lymph flow, decreasing the circulatory volume due to the plasma ultrafiltrate left behind in the interstitium [213]. In the setting of the nephrotic syndrome, with the fall in plasma albumin concentration and oncotic pressure, there is a concomitant fall in interstitial oncotic pressure [214]. Thus there are probably only minor changes in the transcapillary oncotic gradient, and hypoalbuminemia is not the primary step in edema formation. In patients with minimal change disease going into remission with corticosteroid treatment, the maximum recovery diuresis occurs before there has been a substantial increase in plasma albumin concentrations [215]. Dorhout and coworkers [3] found that both plasma and blood volumes decreased in individual patients with minimal-change nephrotic syndrome when they entered remission, providing strong evidence that even (adult) patients with minimal-change nephrotic syndrome were apparently plasma volume expanded during their “nephrotic” phase. Furthermore, they found no correlation between plasma volume and renin activity, or between plasma albumin and blood volume [216]. The lack of a relationship between plasma renin activity and blood volume or between plasma albumin and blood volume is characteristic of both patients with minimal-change nephrotic syndrome and patients with other kidney diseases. The two groups were indistinguishable [216]. These observations raised important questions about the proposed mechanism of edema formation in the nephrotic syndrome.

As indicated earlier, both experimental and human studies have suggested relative resistance to ANP in cases of the nephrotic syndrome. This defect may be due, in part, to increased phosphodiesterase activity in the nephrotic kidney leading to more rapid degradation of cyclic GMP (cGMP), which is the second messenger for ANP. Valentin et al. [217] found that the normal increase in urinary cGMP that follows saline infusion was blunted in nephrotic rats because of increased phosphodiesterase in the inner medullary collecting duct cells. Treatment with a phosphodiesterase inhibitor reverses this defect and restores the normal natriuretic response to volume expansion. Thus an increase in phosphodiesterase activity in the nephrotic syndrome was proposed to accelerate hydrolysis of cGMP resulting in impaired natriuresis. These observations provide a cellular basis for the observations of Perico et al. [202] and Ichikawa et al. [201]. The proteinuric kidney avidly reabsorbs filtered salt in the distal nephron and is not responsive to increased ANP that should normally cause a natriuresis when plasma volume is expanded [201]. In addition, there is increased activity of the sodium−potassium ATPase pump in the cortical collecting duct in nephrotic rats [218].

The management of edema

There is no uniformly recognized treatment regimen for patients with the nephrotic syndrome. The aim of medical management is to reduce the excessive extravascular fluid that has accumulated without decreasing plasma volume below a value necessary for physiologic homeostasis. It is possible for patients with the nephrotic syndrome to become plasma volume contracted. This must be detected, guarded against, and treated. It is, however, impossible to predict the plasma volume of a nephrotic patient by measuring plasma protein or albumin concentration or by measuring plasma renin activity [216]. It is important, therefore, to estimate the intravascular volume state of each patient individually by measuring orthostatic blood pressure, observing neck vein distention, and evaluating the serum urea relative to serum creatinine. Patients who show no evidence of plasma volume contraction should respond to the gentle use of diuretics. Patients who have plasma volume contraction should not be treated with diuretics, but their volume deficit should be treated by bed rest, support hose, or even fluid replacement if necessary.

As indicated earlier, there are two factors responsible for edema in the nephrotic syndrome, and the dominant one in most patients is primary renal sodium retention due to the effect of proteinuria on the ENaC receptor system. Primary treatment beyond focusing on decreasing urinary protein losses by the use of an ACE inhibitor or an ARB as well as modest dietary protein restriction would be dietary sodium restriction to less than 3 g/day and the use of a diuretic. The most commonly used category of diuretics is loop diuretics, such as furosemide or bumetanide [20]. These agents must be bound to albumin for delivery to the loop of Henley via secretion by organic anion transporters [219], and hypoalbuminemia may decrease their effectiveness, both by limiting their absorption in the gut and by reduced transport to the secretory sites as a consequence of low serum albumin concentrations [220]. Infusion of albumin has been used both to increase plasma volume in the event that reduction in plasma volume plays a role in an individual patient and to increase the delivery of loop diuretics, but the effects are of limited value and not recommended [221−223]. Furosemide is generally the most widely used diuretic [224], although it is less effective than bumetanide. In patients who fail to respond to loop diuretics, the most physiologically relevant second agent should be the addition of an ENaC inhibitor such as triamterene [225] or amiloride [226]. Comparison studies are too limited to make firm recommendations.

As indicated earlier, a fraction of nephrotic patients actually has reduced plasma volume as evidenced by increased hematocrit and activation of the renin−angiotensin system. Volume contraction effected by diuretics in this population could potentially increase the risk of reduction in renal perfusion or hemoconcentration which could result in renal insufficiency or thromboembolism [160]. Albumin infusions aiming to increase natriuresis by the suppression of the renin/angiotensin/aldosterone system by volume expansion has not proved to be effective [227,228]. The treatment of edema should consist of restriction of dietary sodium and addition of diuretics as described earlier.

Recommendations for nutritional and nonnutritional treatment of the nephrotic syndrome

The treatment of the nephrotic syndrome begins with identifying the specific cause of the proteinuria and treatment of the underlying disorder, if possible. There are, however, general nutritional and nonnutritional management issues in patients with the nephrotic syndrome per se.

The role of dietary protein modification in the management of the nephrotic syndrome

Dietary protein restriction has been proposed to reduce the rate of progression of renal disease because of the effect of dietary protein on glomerular pressure and other physiological and structural processes [229,230]. The effect of dietary protein restriction on progressive loss of renal function, especially among subjects without significant proteinuria, was not clearly shown to be statistically significant [231,232]. However, increasing dietary protein in patients or in experimental animals with nephrotic range proteinuria has immediate significant adverse effects on proteinuria, causing increased urinary protein loss and reduced serum albumin concentration despite an increase in albumin synthetic rate [28,30]. The major rationale(s) for changing a patient's diet is to blunt manifestations of the syndrome, such as by sodium restriction to address edema and the replacement of nutrients lost in the urine, which may contribute to anemia, bone disease, and other adverse manifestations of the nephrotic syndrome. It might also be possible that specific allergens contained in food may cause renal disease in some patients [233–237]. In this case, dietary modification might prove curative.

Renal blood flow, GFR [55,238,239], and the permselective properties of the glomerular capillary [28,30,49,51] increase quickly following an augmentation in dietary protein intake. Renal hypertrophy also occurs [81,240,241]. Ingestion of protein can result in the release of a cascade of hormones and vasoactive substances, including growth hormone [54], insulin [54], glucagon [242], kinins [243], prostaglandins [50], dopamine [78,244], and insulin-like growth factor-1 [245,246]. In addition, the renin–angiotensin system has been implicated as one of the mediators of protein-induced hyperfiltration [80]. Dietary protein intake stimulates renin secretion [49], and the secondary formation of angiotensin II will, by its effect on efferent arteriolar vasoconstriction, increase intraglomerular capillary pressure and GFR [69].

Proteinuria is responsible for all the manifestations of the nephrotic syndrome: reduced plasma oncotic pressure, edema formation, hyperlipidemia, loss of divalent cations, and anemia. Proteinuria also plays a causative role in the loss of renal function, adding to the effects of the underlying disease that caused the defect in glomerular permselectivity that resulted in the nephrotic syndrome. All therapy must be directed to decrease urinary protein losses. Replacement of urinary protein loss by increasing dietary protein leads to an increase in glomerular permselectivity, which further increases urinary protein losses, primarily by increasing glomerular protein clearance. The net result is a further decline in serum albumin levels [28,30,247] and likely an increase in renal injury mediated by the filtered proteins. Dietary protein should be reduced. Although the absolute target has not been defined, a diet containing 0.8 g/kg/day seems to be a safe target. Clearly high-protein diets are injurious. Pharmacologic intervention should be focused on the inhibition of the renin–angiotensin system by the administration of ACE and/or ARBs [248–250]. Reducing proteinuria decreases a stimulus for renal fibrosis [251] and loss of renal function [252]. Reduction in proteinuria also should reduce serum lipid levels as well as the stimulus for renal salt reabsorption that contributes to edema formation.

ACE inhibitors [172,173] or angiotensin II receptor antagonists have become the mainstay of treatment as a result of evidence from randomized controlled trials and metaanalyses [47,253]. Aldosterone receptor antagonists also reduce proteinuria [254,255]. The effect of spironolactone administration in patients with persistent proteinuria on long-term angiotensin-converting enzyme inhibitor therapy with or without an angiotensin II receptor blocker was investigated in a double-blind, placebo-controlled study. A significant reduction in proteinuria was observed among patients given spironolactone [256]. In another study, Tylicki et al. showed that an aldosterone receptor antagonist in addition to double renin–angiotensin blockade was able to reduce proteinuria and slow the progression of the disease in nondiabetic patients with CKD [257]. In an acute animal model of the nephrotic syndrome, Fukuda et al. showed that blockers of mineralocorticoid receptors and angiotensin II receptors decreased proteinuria and preserved expression of glomerular podocyte protein independently of blood pressure levels [255].

Thus proteinuria can be ameliorated with the use of blockers of the renin–angiotensin–aldosterone system without modification in blood pressure. Treatment with combinations of these blockers reduces proteinuria more effectively than a single drug alone. The use of these agents must be associated with regular monitoring of serum electrolytes, particularly serum potassium, which may increase to hazardous levels, and sodium levels, which may decrease with the use of diuretics. The full antiproteinuric effect of these blockers can take several months to become evident. Independently of these blockers, blood pressure lowering will also reduce proteinuria.

C-C chemokine receptor type 2 has recently been implicated in mediating renal injury and fibrosis associated with proteinuria [258], and blockade of this receptor has been shown to reduce both proteinuria and associated renal fibrosis [259,260], providing an additional pharmacologic target.

Hyperlipidemia

Nephrotic syndrome results in hyperlipidemia and important modifications in lipoprotein and lipid metabolism [261]. Hyperlipidemia in the nephrotic syndrome poses the danger of accelerated atherosclerosis and progressive renal injury. Reduction in plasma lipid levels has been accomplished using such therapies as a low-fat diet [102] and fish oil supplements [175]. Dietary therapy with a low-fat diet, however, is generally of only minimal benefit, and there is no long-term experience with the use of a low-fat diet in the treatment of the hyperlipidemia of the nephrotic syndrome. In addition, there is no compelling reason to prescribe unsaturated fatty acid supplements (such as fish oil) until robust data from randomized controlled studies are available. The general recommendation is to ingest a diet low in cholesterol and saturated fatty acids. It has been shown that reducing proteinuria, using drugs such as ACE inhibitors, lowers blood lipid levels in nephrotic animals [138] and humans [262]. Keilani et al. [262] demonstrated a 10%−20% decrease in the plasma levels of total cholesterol and LDL-cholesterol and Lp(a) with the use of an ACE inhibitor. The magnitude of these changes appears to be related to the degree of reduction in proteinuria. The angiotensin II receptor antagonist, losartan, appears to have a similar beneficial effect on the lipid profile in nephrotic patients [263]. Thus therapy directed at reducing the increased renal clearance of macromolecules has a salutary effect on improving the hyperlipidemia associated with the nephrotic syndrome.

The changes in the metabolism and serum levels of lipoproteins in the nephrotic syndrome are associated with the development and progression of kidney disease and cardiovascular complications [264]. Also, by limiting the lipid flow to muscle to provide energy and to the adipose tissue for energy storage, modifications in the lipid profile may affect the body mass and altered exercise capacity [261].

A study conducted on patients with idiopathic nephrotic syndrome showed that the addition of 20 mg/day of fluvastatin to the basic therapy was associated with a 40% reduction in serum cholesterol levels, a 60% reduction in proteinuria, and a 60% increase in serum albumin levels [265]. Similar results were obtained by Valdivesio et al. after administering 10 mg/day of atorvastatin to 10 dyslipidemic patients who had hypoalbuminemia and proteinuria greater than 3.5 g/24 h [266]. Rayner et al. [264] showed that, in patients with the nephrotic syndrome, the use of a low-lipid diet without pharmaceutical treatment led to a minimal reduction in plasma cholesterol levels, a limited reduction in urinary protein excretion, and normalization of serum albumin levels. Lipid-lowering agents, such as statins [267], probucol [268,269], or gemfibrozil [270], may prove useful in reducing blood lipid levels in these patients [271−273]. The long-term benefits of treatment remain unproven but may include a reduction in cardiovascular risk and preservation of residual renal function. Use of these agents may engender some morbidity, such as rhabdomyolysis with statins [274], especially when given in combination with gemfibrozil [275], and also hepatotoxicity.

It is noteworthy that many nephrotic patients go into remission with the treatment of the underlying disease. Thus identifying and treating the underlying cause of nephrotic syndrome and thereby reducing proteinuria will improve or resolve the dyslipidemia.

Antioxidants

Increased levels of oxidative stress markers have been found in sera and urine of nephrotic children [181] and in animal models of the nephrotic syndrome [276,277]. In children, it was shown that primary nephrotic syndrome is associated with oxidative stress even during remission. This stress may modulate the response to corticosteroids [278]. Pedraza-Chaverri et al. showed that proteinuria, hypoproteinemia, renal dysfunction, and ultrastructural alterations were higher in nephrotic rats fed a deficient diet of antioxidants in contrast to rats treated with vitamin E and selenium [279]. In other studies, after the treatment of nephrotic animals with such antioxidants as catalase or α-tocopherol, a significant reduction of the proteinuria was observed [280−282]. Granqvist et al. described an increase in the plasma antioxidant capacity combined with decreased oxidation of proteins in sera from nephrotic rats [283]. This observation suggests that oxidative damage to glomerular cells may contribute to the progressive renal injury in the nephrotic syndrome [283]. Recently, Sutariya et al. found that a natural bioactive compound named α-asarone, which has been shown to have protective properties against doxorubicin-induced nephrotic syndrome, when administered in an animal model of nephrotic syndrome, restored antioxidant enzyme activities in kidney tissue [284]. These data should be considered preliminary, and we expect more information from future experimental studies.

In conclusion, the use of antioxidant medicines in the nephrotic syndrome appears useful, but large clinical trials to ascertain their effectiveness and safety in nephrotic patients are still lacking.

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CHAPTER

29

Nutritional approaches and plant-dominant diets for conservative and preservative management of chronic kidney disease

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Introduction

Chronic kidney disease (CKD) is closely related to nutritional status and diet [1]. Altered protein and energy homeostasis, abnormal protein catabolism, acid–base derangements, and hormonal dysfunction all affect the nutritional status of patients with kidney disease. In children, growth and development are hindered [2]. Accumulation of nitrogen-containing products from dietary and intrinsic protein catabolism may distort taste and smell and blunt appetite [2]. Nutrient absorption through the gastrointestinal (GI) tract becomes abnormal, as uremia affects the microbiome and disrupts intestinal epithelia [3]. Muscle and fat wasting often develop, exacerbated by the comorbid conditions and frailty inherent to the advanced age of many CKD patients. Hence, nutritional status often becomes disordered, and protein-energy wasting (PEW) is common, justifying the need for dietary adjustments in this population. Nutritional therapy may help manage uremia, as well as other complications such as electrolyte and acid–base imbalances, fluid and salt retention, mineral and bone disorders, and failure to thrive. Dietary interventions may also be used for the conservative management of uremia when the transition to dialysis needs to be delayed or avoided. It is possible, though not yet unequivocally proven, that such nutritional interventions may also slow the rate of disease progression, independent of uremia management. Given that approximately 10% of the adult population globally has CKD [4], and considering the exceptionally high costs of maintenance dialysis therapy and kidney transplantation, supportive management of CKD via dietary interventions may offer a feasible and economical alternative.

Dietary protein in kidney disease

It is unclear whether quantity or quality of ingested protein is a risk factor for incident kidney disease. Evidence suggests that daily dietary protein intake (DPI) exceeding 1.5 g/kg of ideal body weight (g/kg/d) may cause glomerular hyperfiltration [5] and proinflammatory gene expression [6], both known risk factors for kidney disease, as in the diabetic nephropathy model [7]. A high-protein diet exacerbates proteinuria in persons with diabetes or hypertension [8], but as a popular weight reduction strategy its net effect on kidney health is unclear.

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Animal models have consistently demonstrated that low protein intake constricts the glomerular *afferent* arterioles, whereas they dilate in nephropathies as a compensatory mechanism to rise intraglomerular pressure, which increases glomerular filtration [9]. Over time, the glomerular hyperfiltration damages the remaining glomeruli [6]. Thus a low-protein diet (LPD) has a preglomerular effect that can enhance the postglomerular effect of angiotensin pathway modulators that lower intraglomerular pressure by dilating the *efferent* arterioles (Fig. 29.1) [11]. Human studies of dietary protein restriction, however, have been less consistent. The *Modification of Diet in Renal Diseases* (MDRD) study reported that the progression of kidney disease was only minimally decelerated by an LPD [12]. Several limitations of the MDRD study should be noted [13]. Most other controlled trials have confirmed beneficial effects of restricted protein intake as did several metaanalyses that included the MDRD study [14].

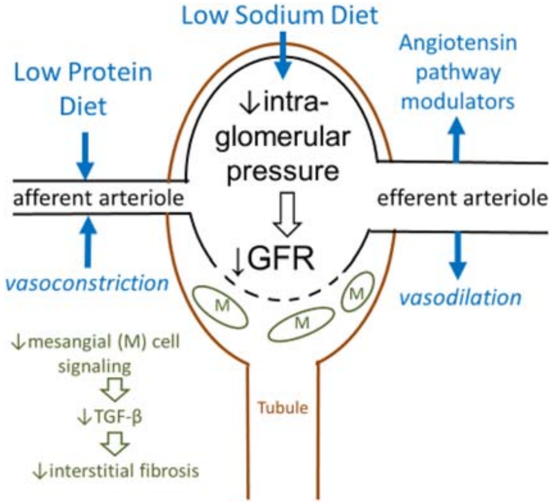

FIGURE 29.1 *The effects of a low-protein and low-salt diet on afferent arteriole contraction leading to reduced intraglomerular pressure.* By contracting the afferent arteriole and lowering intraglomerular pressure, a low-protein diet results in incrementally lowered GFR, but in the long term it diminishes the damage to the glomerulus structure and function. A potential secondary effect of lowered intraglomerular pressure is mitigated mesangial (M) cell signaling leading to lower TGF-β expression and reduced interstitial fibrosis. These renoprotective effects of a low-protein diet can be synergistic with the direct effect of low-sodium diet as well as the effect of angiotensin pathway modulators (angiotensin converting enzyme inhibitors and angiotensin receptor blocker agents) in dilating the efferent arteriole and thereby more effectively reducing intraglomerular pressure and glomerular damage. On the contrary, a high-protein diet dilates *afferent* arteriole and elevates intraglomerular pressure leading to increased GFR in short term, while the glomerular hyperfiltration stimulates M cell signaling leading to increased TGF-β release and subsequent progressive fibrosis and renal damage in long term. *GFR*, Glomerular filtration rate. Source*: Adapted from Ko GJ, Rhee CM, Kalantar-Zadeh K, Joshi S. The effects of high-protein diets on kidney health and longevity. J Am Soc Nephrol 2020;31(8):1667–79. https://doi.org/10.1681/ASN.2020010028. PubMed PMID: 32669325; PMCID: PMC7460905. https://www.ncbi.nlm.nih.gov/pubmed/32669325 [10].*

Current evidence suggests that an LPD mitigates proteinuria in both experimental [5] and human kidney disease models [15]. The proteinuria amelioration is likely related to the reduction in intraglomerular pressure (Fig. 29.1) [11]. This favorable effect is independent of angiotensin pathway modulation [11] and holds even in nephrotic ranges of proteinuria [16] and in earlier stages prior to the development of renal insufficiency, particularly if the patient was previously consuming a high-protein diet [11,17].

Restricting dietary protein also results in a proportional reduction in urea generation [18]. After breakdown of protein, individual amino acids are deaminated by the removal of an α-amino group, leaving a carbon skeleton ketoacids, which can be recycled to form other amino acids and proteins or can be used for energy generation via the tricarboxylic acid cycle [19], while urea is generated through the urea cycle (Fig. 29.2). Persistently high blood urea concentrations, called *azotemia*, a commonly used marker for *uremia*, may enhance protein carbamylation and generate reactive oxygen species leading to oxidative stress, inflammation, endothelial dysfunction, and cardiovascular (CV) disease [20]. This process is decreased by decreasing protein intake in the diet. Ameliorating azotemia by eating less protein results in parallel reductions of other nitrogenous compounds that act as putative uremic toxins [21]. Although uremic symptoms diminish by eating less protein, there are limited studies that have examined the effectiveness and safety of the LPD as a means to defer or avoid transition to dialysis therapy [22,23].

Among different ranges of low protein intake the 0.6–0.8 g/kg/d range is the most frequently recommended target for patients with moderate-to-advanced kidney disease [estimated glomerular filtration rate (eGFR) <45 mL/min/1.73 m^2] and for the management of substantial proteinuria (>0.3 g/d), whereas the so-called very LPD (<0.6 g/kg/d) supplemented with essential amino acids or their ketoacids is also used [24]. People at higher risk of kidney disease such as those after donor or cancer nephrectomy, diabetes mellitus, or hypertension may benefit from a modest protein intake of <1 g/kg/d to maintain a moderately low intraglomerular pressure [25]. Safety and feasibility of low protein intake, risk of PEW, and patient adherence to dietary restrictions are among the main concerns (Table 29.1) [26]. The *recommended dietary allowance* (RDA) for protein is 0.8 g/kg/d, while 0.66 g/kg/d is the *estimated average requirement* for otherwise healthy adults; hence, a diet consisting of 0.6–0.8 g/kg/d fulfills dietary needs. Clinical trials of LPD s administered at the lower threshold (0.6 g/kg/

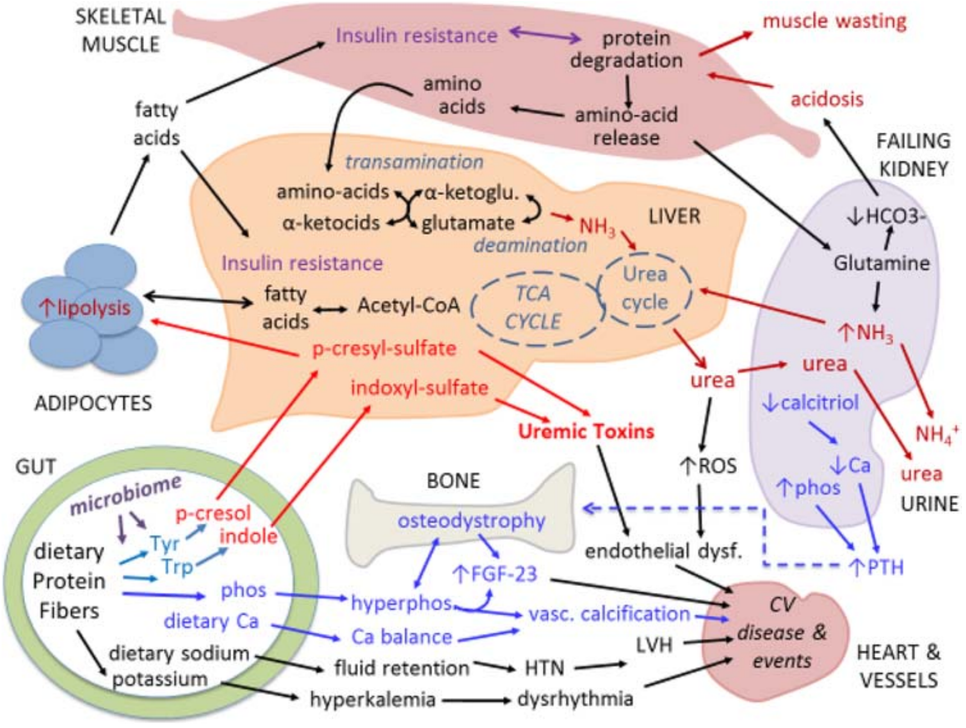
SKELETAL MUSCLE
Insulin resistance
protein degradation
muscle wasting
amino acids
amino-acid release
acidosis
fatty acids
FAILING KIDNEY
transamination
amino-acids
α-ketoglu.
α-ketocids
glutamate
NH3
LIVER
deamination
↓HCO3-
Glutamine
Insulin resistance
Urea cycle
TCA CYCLE
↑lipolysis
fatty acids
Acetyl-CoA
↑NH3
p-cresyl-sulfate
urea
urea
indoxyl-sulfate
↓calcitriol
NH4+
ADIPOCYTES
Uremic Toxins
↓Ca
GUT
↑ROS
urea
microbiome
BONE
↑phos
URINE
p-cresol
indole
osteodystrophy
Tyr
Trp
dietary Protein Fibers
endothelial dysf.
↑PTH
↑FGF-23
phos
hyperphos.
CV disease & events
dietary Ca
vasc. calcification
Ca balance
LVH
HEART & VESSELS
dietary sodium potassium
fluid retention
HTN
hyperkalemia
dysrhythmia

FIGURE 29.2 *Relevant metabolic pathways related to protein and amino acid metabolism in chronic kidney disease*. The TCA relates to a series of chemical reactions that can metabolize amino acids. Amino groups are the products of amino acid deamination. Urea is synthesized through the urea cycle in the liver from the oxidation of amino acids or from ammonia. These mechanisms serve to trap and neutralize the highly volatile and toxic ammonia that is released from α-amino groups upon the transamination of amino acids in the liver. *Acetyl-CoA*, Acetyl coenzyme A; *Ca*, calcium; *FGF-23*, fibroblast growth factor 23; *HTN*, hypertension; *NH_3*, ammonia; *NH_4^+*, ammonium; *phos.*, phosphorus; *PTH*, parathyroid hormone; *ROS*, reactive oxygen species; *TCA*, tricarboxylic acid; *Trp*, tryptophan; *Tyr*, tyrosine; *vascular dys.*, vascular dysfunction; *α-ketoglu.*, α-ketoglutaric acid.

d) or even less such as the MDRD study have rarely, if ever, reported deterioration of nutritional status [12,26]. However, in most children as well as in adults at higher risk of malnutrition, higher protein intake closer to 0.8 g/kg/d may be necessary to assure appropriate growth and development and to prevent or correct PEW. The safety and adherence to an LPD can be improved by provision of adequate energy of 30–35 Cal/kg/d and ongoing nutritional education and surveillance [27,28].

High-protein diets may be harmful to kidney health

While the United States National Academy of Medicine has maintained that RDA of DPI should be 0.8 g/kg of the ideal body weight per day (g/kg/d), Americans on average consume much higher amounts of protein, that is, 1.2–1.4 g/kg/d, mostly from animal sources, according to analyses from the National Health and Nutrition Examination Survey (NHANES) [29]. In recent practice, higher DPI has been recommended to combat obesity and diabetes [30,31], despite recent data suggesting higher risk of CKD incidence and progression with higher DPI, especially from red meat [32–34]. Ketogenic (keto)-diets, which are also high in protein and animal fats, are gaining popularity across different health-care systems throughout the world as a recommended dietary intervention for adults with diabetes [35]. Despite its immediate appeal for the use of type 2 diabetes, the keto-diet has not been as effective for glycemic control or weight loss in randomized, controlled trials as often touted and may carry additional risks to long-term health [36]. Further, previous and emerging data suggest that high DPI in these diets, by the way of causing increased intraglomerular pressure with resultant glomerular hyperfiltration, may adversely affect kidney health over time across populations with or at-risk for CKD [10,32].

An LPD preserves kidney function

The scientific premise for low DPI targets was presented in a recent critical review and metaanalysis of 16 dietary trials with more than 30 CKD patients in each trial (Fig. 29.3) [37] and also discussed in a 2017

TABLE 29.1 Potential benefits and challenges of a 0.6–0.8 g/kg/d low-protein diet (LPD) in the nutritional management of chronic kidney disease (CKD)[a].

	Potential benefits	Challenges and risks	Additional comments
CKD progression	Synergistic effect with angiotensin pathway modulators[b] to lower intraglomerular pressure	In the first several months a slight drop in GFR may be observed as shown in the MDRD study[c]	Inconclusive results in the MDRD study, but a small effect size in metaanalyses[d]
Effect on proteinuria	Consistent antiproteinuric effect may improve hypoalbuminemia	Contrary to the notion that a higher DPI is needed to replace urinary protein loss	Some data suggest that even larger effect may be achieved by DPI of <0.6 g/kg/d
Uremia management and deferral of dialysis initiation	Consistent and biologically plausible data for almost a century	Unlikely to worsen uremia but potential risk of resurfacing or exacerbating PEW	Patients at higher risk of PEW may benefit from supplements, including EAA or KA
Metabolic acidosis	Lower H^+ generation is proportional to less DPI, especially with larger vegetarian food proportion	The need for >50% HBV may prompt higher nonvegetarian foods that are more acidogenic	While >50% HBV protein is recommended, the remainder can be plant-based foods
Mineral and bone disease	Inherently lower phosphorus content of LPD improves mineral bone disease parameters, including sHPT and high FGF-23	Higher calcium content in some KA preparations may worsen calcium loads	Additional improvements in bone health by alleviating acidosis can be achieved
PEW	Improving hypoalbuminemia in proteinuric patients may help neutralize circulating inflammatory compounds	Weight loss may occur. LPD-intake patterns may continue following thrice-weekly hemodialysis therapy when higher protein intake is recommended	Use HBV as 50% of the source of dietary protein. Liberalize diet during PEW correction episodes (see Table 29.2)
Cardiovascular and metabolic health	Lower protein intake is associated with lower dietary salt and potassium and may be less atherogenic given higher proportion of vegetarian food	Higher dietary fat intake (to achieve DEI 30–35 Cal/kg/d) may confound the goal of achieving a heart-healthy diet profile	Higher proportions of unsaturated fat and complex carbohydrates are recommended (see Table 29.2 and text)
Glycemic control and insulin response	Improvement in insulin resistance is likely	Higher carbohydrate and fat intake (to achieve DEI >30–35 Cal/kg/d) may worsen glycemic control in LPD or VLPD	Given increased insulin-half-life and burnt-out diabetes with CKD progression, preventing hypoglycemic episodes are prudent
Quality of life and adherence	High degree of patient centeredness given that many CKD patients proactively seek nutritional therapies and dietary advice	Challenges with adherence, diet fatigue, poor palatability, and cravings are reported	Recommend creative recipes and strategies to engage patients
Mortality	No convincing data to suggest improved survival, although dialysis therapy deferral is a potential mechanism given high early dialysis death	Highly unlikely to cause higher death risk with DPI 0.6–0.8 g/kg/d unless severe PEW emerge and remain uncorrected	Consider supplements or other corrective strategies whenever PEW is suspected or diagnosed
Hypertension management	MDRD and other data suggest improved BP control	Less likely to increase BP given inherently lower salt intake	Lower salt intake may be a potential mechanism
Microbiome modulation	Improved microbiome profile may be achieved by less uremic toxin generation	Less likely to promote an unfavorable microbiome milieu	Uremia per se can lead to an unfavorable microbiome

[a] *See examples of meals/recipes based on the suggested ranges and recommendations.*
[b] *Angiotensin pathway modulators include ACE inhibitors and ARB.*
[c] *The MDRD study data were originally presented by Klahr et al. [12] with additional analyses by Levey et al. [13].*
[d] *Metaanalyses by Kasiske et al. show a statistically significant but rather small effect size of LPD in slowing the CKD progression rate [14].*
ACE, Angiotensin-converting enzyme; *ARB*, angiotensin receptor blockers; *BP*, blood pressure; *DEI*, dietary energy intake; *DPI*, dietary protein intake; *EAA*, essential amino acids; *FGF-23*, fibroblast growth factor-23; *GFR*, glomerular filtration rate; *HBV*, high biologic value protein; *KA*, ketoacids (keto-analogs of amino acids); *MDRD*, Modification of Diet in Renal Disease; *PEW*, protein-energy wasting; *sHPT*, secondary hyperparathyroidism; *sVLPD*, supplemented VLPD; *VLPD*, very low protein diet.

New England Journal of Medicine review paper [1]. These data highlight the utility of LPD for the management of CKD (Table 29.2), suggesting that an LPD of 0.6–0.8 g/kg/d versus higher amounts is associated with lower ESKD risk, higher serum bicarbonate and lower serum phosphorus levels, less azotemia, and lower mortality trends [37]. Whereas we and others have recommended DPI of 0.6–0.8 g/kg/d, some other

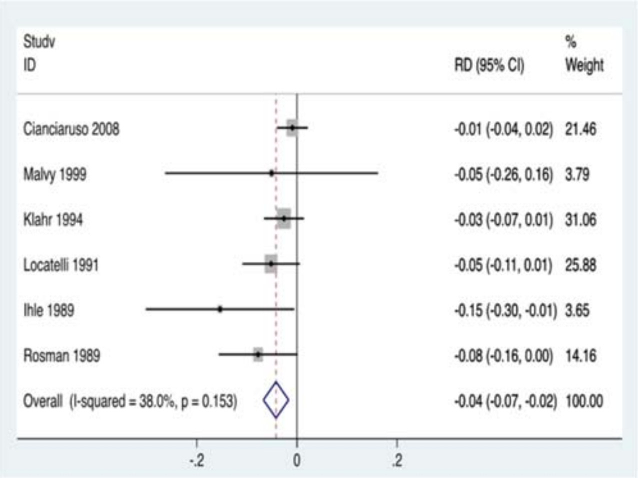

FIGURE 29.3 Metaanalysis of the randomized controlled trials with low-protein diet suggesting efficacy of diet in lowering the risk of kidney failure. This metaanalysis includes 6 (out of 16) randomized control trials of low-protein diet. Source*: Adapted from Rhee CM, Ahmadi SF, Kovesdy CP, Kalantar-Zadeh K. Low-protein diet for conservative management of chronic kidney disease: a systematic review and meta-analysis of controlled trials. J Cachexia Sarcopenia Muscle 2018; 9(2):235–45. https://doi.org/10.1002/jcsm.12264. PubMed PMID: 29094800; PMCID: PMC5879959. https://www.ncbi.nlm.nih.gov/pubmed/29094800*.

investigators, including Metzger et al. [53], showed that a DPI of <0.6 g/kg/d may result in even slower CKD progression; however, a DPI of 0.6–0.8 g/kg/d is considered the most pragmatic and safest target when used without amino acid or keto-analog supplements to avoid PEW. For persons without established CKD but who are at a high risk of CKD, such as those with a solitary kidney or diabetic glomerular hyperfiltration, it is recommended that a high DPI >1.0 g/kg/d should be avoided [54], especially since patients with diabetes develop more severe hyperfiltration in response to high DPI [55].

Plant-based foods have a favorable impact on kidney health

The typical American diet contains 15%–20% protein with less than one-third of protein sources from plants [56]. While human trials on the effects of high protein intake have yield mixed findings, animal models are relatively consistent with evidence of histological damage, including a 60%–70% increase in renal and glomerular volumes, 55% more fibrosis, and 30% more glomerulosclerosis [57]. A recent comprehensive and critical review of the literature concluded that daily red meat consumption over years may increase CKD risk, whereas fruit and vegetable proteins may be renal protective [33]. Prior studies summarized by some of the authors of this article [54,58–62] and others [63–66] suggest that animal-based protein is harmful to kidney health, while a plant-dominant diet may slow CKD progression. A landmark study was presented by Kontessis et al. [67] who studied volunteers fed for 3 weeks with a vegetable-based diet ($N = 10$), an animal protein diet ($N = 10$), or an animal protein diet supplemented with fiber ($N = 7$), all with the same amount of total protein; animal-based protein diets increased glomerular filtration rate (GFR) more than similar amounts of plant-based proteins, that is, higher glomerular hyperfiltration was observed with more meat and less vegetable-derived proteins [67]. Other important studies supporting the benefit of a plant-dominant diet in slowing CKD progression include the study by Lin et al. [68] (examined 3348 women in the Nurses' Health Study and found that the highest quartile of meat intake was associated with 72% higher risk of microalbuminuria), Kim et al. [69] (showed that in 14,686 middle-aged adults, higher adherence to a plant-based diet was associated with favorable kidney outcomes), Haring et al. [70] (showed that red and processed meat were associated with higher CKD risk, while nuts, low-fat dairy products, and legumes were protective against the development of CKD), and Chen et al. [71] (showed lower mortality in CKD patients on diet with higher plant sources).

Benefits of a plant-dominant LPD

We have defined a plant-dominant LPD, also referred to as PLADO, as a type of LPD with DPI of 0.6–0.8 g/kg/d with at least 50% plant-based sources to meet the targeted dietary protein, and which should preferably be whole, unrefined, and unprocessed foods (Fig. 29.4) [72]. This is consistent with the RDA of DPI of 0.8 g/kg/d, which has a high safety margin, given that based on established metabolic studies [73] the lowest DPI requirement to avoid catabolic changes is 0.45–0.5 g/kg/d. It has been previously suggested that ≥50% of DPI should be of "high biologic value" with high GI absorbability to ensure adequate intake of essential amino acids while on LPD [74]. However, other metrics, including the "protein digestibility-corrected amino-acid score," which is a more accurate method recommended by the Food and Agricultural Organization and the World Health Organization, grant high scores to many plant-based sources and may be a more appropriate measure of protein quality [75]. Other features of PLADO include relatively low sodium intake <3 g/d, higher dietary fiber of at least 25–30 g/d, and adequate dietary energy intake (DEI)

TABLE 29.2 Low-protein diet (LPD) controlled trials with greater than 30 participants in each study [1].

Reference	Participants	Diet (g/kg/d)	Duration of follow up	Results
Rosman [38,39]	247 CKD 3–5 pts	0.90–0.95 versus 0.70–0.80 versus unrestricted	4 yrs	Significant CKD slowing in LPD in male pts
Ihle [40]	72 CKD 4–5 pts	LPD (0.6) versus higher DPI (0.8)	18 mo	Loss of GFR in control versus LPD ($P < .05$). Wt loss
Lindenau [41]	40 CKD 5 pts	LPD versus sVLPD (0.4) w KA	12 mo	Decreased phos. with sVLPD and improved bone health
Williams [42]	95 CKD 4–5 pts	LPD (0.7) versus 1.02–1.14	18 mo	No differences, minor Wt loss
Locatelli [43]	456 CKD 3–4 pts	0.78 versus 0.9	2 yrs	Trend for difference in renal outcomes ($P = .059$)
MDRD Klahr [12]	585 CKD 3–4 pts	1.3 versus 0.6	27 mo	No difference in GFR decline at 3 years
Montes-Delgado [44]	33 CKD 3–5 pts	LPD versus suppl. LPD	6 mo	Slower eGFR decline with supplements
Malvy [45]	50 CKD 4–5 pts	sVLPD (0.3) KA versus LPD (0.65)	3 yrs	Decreased SUN lean body mass and fat in sVLPD
Teplan [46]	105 CKD 3b–4 pts	LPD w versus w/o KA	3 yrs	Slower CKD progression
Prakash [47]	34 CKD 3b–4 pts	0.6 versus 0.3 w KA	9 mo	Faster decline in LPD
Brunori [23]	56 >70 yrs old CKD 5 pts	sVLPD (0.30) w KA versus dialysis	27 mo	Similar survival but more hospitalizations in dialysis
Mircescu [48]	53 CKD 4–5 pts	sVLPD (0.3) vegan w KA versus LPD	48 wks	Less dialysis initiation in sVLDP
Cianciaruso [49]	423 CKD 4–5 pts	0.55 versus 0.80	18 mo	Reduced urinary urea, Na, phos
Di Iorio [50]	32 CKD w proteinuria	VLPD versus LPD	6 mo	58% greater reduction in proteinuria
Jiang [51,52]	60 PD w RKF	LPD versus sLPD w KA versus HPD	12 mo	RKF decreased in the LPD and HPD
Garneata [24]	207 CKD 4–5 pts	LPD (0.6) versus sVLPD w KA	15 mo	Less dialysis initiation

CKD, Chronic kidney disease; *DPI*, dietary protein intake; *eGFR*, estimated glomerular filtration rate; *KA*, ketoacids (keto-analogs of amino acids); *mo*, months; *phos.*, phosphorus; *pts*, patients; *SUN*, serum urea nitrogen; *sVLPD*, supplemented VLPD; *VLPD*, very low protein diet; *Wt*, weight; *yrs*, years.

of 30–35 Cal/kg/d, assuming that the DEI calculations are based on the ideal body weight, similar to the approach to calculating DPI (Fig. 29.4).

There are multiple pathways by which an LPD with at least 50% plant-based protein sources ameliorates CKD progression, in addition to reducing glomerular hyperfiltration [58] (Table 29.3):

1. Reduction in nitrogenous compounds leads to less production of ammonia and uremic toxins as an effective strategy in controlling uremia and delaying dialysis initiation [37].
2. Synergism with renin–angiotensin–aldosterone system and SGLT2 inhibitors, since LPD reinforces the pharmaco-therapeutic effect of lowering intraglomerular pressure through complementary mechanisms (Fig. 29.1) [76].
3. Attenuation of metabolites derived from gut bacteria that are linked with CKD and CV disease: Animal protein ingredients, including choline and carnitine, are converted by gut flora into trimethylamine (TMA) and TMA N-oxide (TMAO) that are associated with atherosclerosis, renal fibrosis [77], and increased risk of CV disease and death [78]. The favorable impact on the gut microbiome [79] similarly leads to lower levels of other uremic toxins such as indoxyl sulfate and *p*-cresol sulfate [80].
4. Decreased acid load: Plant foods have a lower acidogenicity in contrast to animal foods, and this alkalization may have additional effects beyond mere intake of natural alkali [81].
5. Reduced phosphorus burden: There is less absorbable phosphorus in plant-based proteins

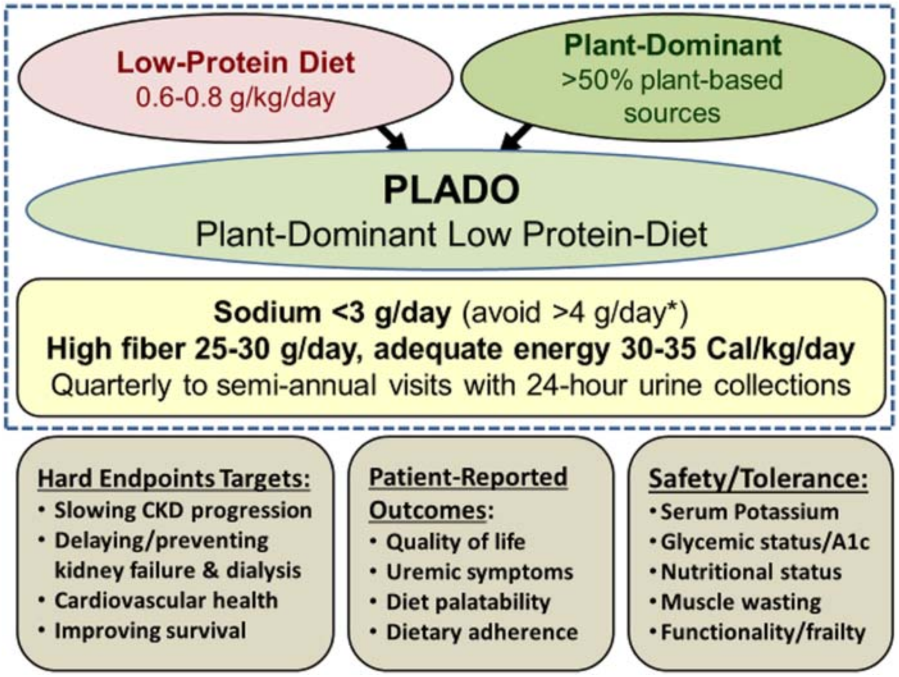
Low-Protein Diet
0.6-0.8 g/kg/day
Plant-Dominant
>50% plant-based sources
PLADO
Plant-Dominant Low Protein-Diet
Sodium <3 g/day (avoid >4 g/day*)
High fiber 25-30 g/day, adequate energy 30-35 Cal/kg/day
Quarterly to semi-annual visits with 24-hour urine collections
Hard Endpoints Targets:
• Slowing CKD progression
• Delaying/preventing kidney failure & dialysis
• Cardiovascular health
• Improving survival
Patient-Reported Outcomes:
• Quality of life
• Uremic symptoms
• Diet palatability
• Dietary adherence
Safety/Tolerance:
• Serum Potassium
• Glycemic status/A1c
• Nutritional status
• Muscle wasting
• Functionality/frailty

FIGURE 29.4 Overview of the PLADO for nutritional management of CKD, based on a total dietary intake of 0.6–0.8 g/kg/d with >50% plant-based sources, preferentially unprocessed foods, relatively low dietary sodium intake <3 g/d (but the patient can target to avoid >4 g/d if no edema with well-controlled hypertension), higher dietary fiber of at least 25–30 g/d, and adequate dietary energy intake of 30–35 Cal/kg/d. Weight is based on the ideal body weight. Note that serum B12 should be monitored after 3 years of vegan dieting. *CKD*, Chronic kidney disease; *PLADO*, plant-dominant low-protein diet. Source: *Adapted from Kalantar-Zadeh K, Joshi S, Schlueter R, Cooke J, Brown-Tortorici A, Donnelly M, et al. Plant-dominant low-protein diet for conservative management of chronic kidney disease. Nutrients 2020;12(7). https://doi.org/10.3390/nu12071931. PubMed PMID: 32610641; PMCID: PMC7400005. https://www.ncbi.nlm.nih.gov/pubmed/32610641.*

TABLE 29.3 Benefits and challenges of low-protein diet (LPD) with >50% plant-based protein sources.

Benefits of LPD with >50% plant sources	Potential challenges of LPD
• Lowering intraglomerular pressure	• Risk of PEW
• Synergistic effect with RAASi and SGLT2i	• Inadequate essential amino acids
• Controlling uremia and delaying dialysis	• Undermining obesity management
• Preventing cardiovascular harms of meat	• High glycemic index
• Less absorbable phosphorus	• High potassium load and hyperkalemia
• Lowering acid load with less acidogenicity	• Low palatability and adherence
• High dietary fiber enhancing GI motility	• Inadequate fish intake if vegan
• Favorable changes in microbiome	
• Less TMAO leading to less kidney fibrosis	
• Less inflammation and oxidative stress	

GI, Gastrointestinal; *PEW*, protein-energy wasting; *RAASi*, renin–angiotensin–aldosterone system inhibitors; *TMAO*, TMA N-oxide.

given the presence of indigestible phytate binding to plant-based phosphorus. Fruits and vegetables are less likely to have added phosphorus-based preservatives that are often used for meat processing [64,82–84].

6. Modulation of advanced glycation end (AGE) products: Higher dietary fiber intake results in a favorable modulation of AGE [85] which can slow CKD progression [86], enhance GI motility, and lower the likelihood of constipation that is a likely contributor to hyperkalemia.
7. Favorable effects on potassium metabolism: A plant-based diet based on more whole fruits and vegetables lessens the likelihood of potassium-based additives that are often found in meat products [87,88].
8. Antiinflammatory and antioxidant effects: There is a decreased risk of CKD progression and CV disease due to higher intake of natural antiinflammatory and antioxidant ingredients, including carotenoids, tocopherols, and ascorbic acid [89,90].

Features of PLADO regimens

As stated earlier, the plant-dominant restricted protein diet consists of an LPD amounting to 0.6–0.8 g/kg/d with at least 50% of the dietary protein being from plant-based sources. Table 29.4 compares PLADO with a standard diet in the United States, in that the total amount and proportion of plant-based protein is usually 1.2–1.4 g/kg/d and 20%–30%, respectively, whereas the

TABLE 29.4 Comparing low-protein diet (LPD) >50% plant-based protein sources.

Protein metric	Standard diet	LPD >50% plant-based sources (PLADO)
Proportion of plant-based protein (%)	20%–30%	50%–70%[a]
Total protein per kg IBW (g/kg/d)	>0.8, usually 1.2–1.4	0.6–0.8
Total protein intake (g/d)	96–112 g	48–64 g
Protein density (g/100 Cal)	4.4–5.1	2.2–2.9
Proportion of energy from protein (%)	16%–19%	8%–11%
Total plant-based protein (g/d)	24–34	24–45
Total animal-based protein (g/d)	68–83	14–32 (or none[a])

[a] *Up to 100% vegan is allowed based on patient choice.*

Known as PLADO versus standard diet, based on 2400 Cal/d in an 80-kg person.

PLADO not only has less total protein of 0.6–0.8 g/kg/d but it also includes 50%–70% of plant-based sources for this restricted DPI goal. Hence, an 80-kg person with CKD, for instance, would be recommended to have 46–64 g of DPI per day, out of which 24–45 g will be from plant-based sources, while the rest is according to patient choice and preferences. As shown in Table 29.4, the total amount of animal-based protein under PLADO regimen is 14–32 g/d, which is less than half of the 68–83 g/d in the standard diet, but the patient also has the choice of being nearly or totally plant-based. There are different types of vegetarian diets [58]: (1) vegan, or strict vegetarian (100% plant-based), diets that not only exclude meat, poultry, and seafood but also eggs and dairy products; (2) lacto- and/or ovo-vegetarian diets that may include dairy products and/or eggs; (3) pesco-vegetarian diets that include a vegetarian diet combined with occasional intake of some or all types of seafoods, mostly fish; and (4) flexitarians, which is mostly vegetarian of any of the previous types with occasional inclusion of meat. The PLADO does NOT require adherence to any of these strict diets, but is a flexible LPD of 0.6–0.8 g/kg/d range with 50% or more plant-based sources of protein based on the patient's choice (Table 29.4). Whereas some nephrologists may promote a pesco–lacto–ovo-vegetarian LPD with >50% plant sources, patients have the ultimate discretion to decide about the non-plant-based portion of the protein ad lib. Based on our decades-old experience in running LPD clinics, most CKD patients will adhere to 50%–70% plant-based sources, while some may choose >70% or strictly plant-based diets.

Safety and adequacy of a PLADO

Potential challenges of PLADO are outlined in Table 29.3, which will be largely related to the adequacy and safety of this type of dietary management of CKD patients. The risks of PEW and sarcopenia are the leading concerns, although there is little evidence for these sequelae. As discussed earlier and based on the US-recommended RDA for safe DPI ranges, it is highly unlikely that the targeted DPI of 0.6–0.8 g/kg/d with >50% plant sources will engender PEW in clinically stable individuals. No PEW was reported in 16 LPD trials cited earlier [37,73], including the MDRD trial [73], although PEW per se is a risk of poor CKD outcomes, including faster CKD progression [91]. However, it is prudent that in patients who may develop signs of PEW or acute kidney injury (AKI), higher DPI targets should be temporarily used until PEW or AKI is resolved. On the other hand, if there is concern related to the likelihood of obesity and hyperglycemia, patients and providers should be reassured that LPD therapy in CKD has not been shown to be associated with such risks, and indeed an LPD with plant-based sources has salutary effects on insulin resistance and glycemic index, as long as total calorie intake remains within the targeted range of 30–35 kcal/kg/d [59,60].

Another frequently stated concern is the perceived risk of hyperkalemia. We are not aware of scientific evidence to support the cultural dogma that dietary potassium restriction in CKD improves outcomes [92]. Evidence suggests that dietary potassium, particularly from whole-, plant-based foods, does not correlate closely with serum potassium variability [93,94]. Indeed, a high-fiber diet enhances bowel motility and likely prevents higher potassium absorption, and alkalization with plant-based dietary sources also lowers the risk of hyperkalemia [95–99]. Of note, dried-fruit, juices, smoothies, and sauces of fruits and vegetables require additional consideration given their high potassium concentrations. Moreover, newly available potassium binders, which were not FDA-approved during the era of prior LPD trials such as the MDRD, may be used in the contemporary management of CKD patients at the discretion of clinicians [100].

Diet palatability and adherence to LPD or meatless diets are often cited as dietary management challenges. Based on our extensive experience in running patient-centered LPD clinics for hundreds of CKD patients [74], and given prior data on dietary adherence research [74,101], the suggested PLADO with DPI of 0.6–0.8 g/kg/d and >50% plant-based sources is feasible and well accepted among patients with CKD [74]. Patients have the opportunity to choose the contribution of protein plant sources between 50% and 75% or >75%, and these two strata along with palatability, appetite [102], and adherence should be monitored closely in CKD clinics. Concerns about B12 deficiency associated with meatless diets can be mitigated by the use of oral supplements as needed [103].

Impact of PLADO on microbiome in CKD

Eating a plant-dominant, fiber-rich LPD may lead to favorable alterations in the gut microbiome, which can modulate uremic toxin generation and slow CKD progression, along with reducing CV risk in CKD patients [1,104–106]. Uremic plasma impairs barrier function and depletes the tight junction protein constituents of intestinal epithelium [107]. The influx of retained uremic solutes from the bloodstream per se induces changes in the microbial population simultaneously with gut wall inflammation and breakdown of epithelial junctions [108–119]. Bacteria-derived toxins then translocate back across the leaky gut barrier into the systemic circulation and promote inflammation and multiorgan dysfunction [108,120]. At least five major gut-derived uremic toxins have been associated with CV disease and mortality in CKD: indoxyl sulfate, indole-3 acetic acid, *p*-cresol sulfate, TMAO, and phenylacetylglutamine [120]. In a small study that included nine CKD patients per group, and which had a short duration of 6 months, LPD with or without inulin prebiotic supplementation was reported to modify the gut microbiome, increase serum bicarbonate, and improve physical function scores [121], but the investigators did not examine CKD progression or levels of gut-derived uremic toxins. Future studies should examine the role of PLADO regimens on gut microbiome in CKD patients.

Similarities and distinctions between PLADO and other CKD diets

In contrast to other diets used for the management of CKD, the PLADO offers a more pragmatic and patient-centered nutritional management which is aligned with contemporary dietary management goals. Unlike the diets used in the MDRD study and other studies that focused on hard outcomes, the premise of PLADO is based on its expected effects on both hard endpoints and patient-centered outcomes, including health-related quality of life, uremic symptoms, and diet palatability, while safety and adequacy remain among important goals. It is important to note that the MDRD study was conducted in the early 1990s under dietary practices that are not relevant to contemporary practice. While high-protein diets such as keto, Atkins, and Paleo are popular in contemporary culture, there has been growing interest in plant-based diets across the lay and scientific communities and professional societies, including the National Kidney Foundation [122], which were not considered in the MDRD study.

Restricted protein diets that are partially to entirely plant-based are more broadly generalizable to the adult populations as compared to the prior LPD trials, including the MDRD study. PLADO can be safely recommended to both patients with early CKD, including those with any degree of proteinuria regardless of etiology [123], as well as to late-stage CKD populations, including those with an eGFR <45 mL/min/1.73 m^2, without a lower eGFR limit, to take the advantage of the effects of LPDs in controlling uremia and averting the need for dialysis. This stands in sharp contrast to the MDRD study, participants of which had relatively high eGFRs (eGFR 25–55 mL/min/1.73 m^2), and which focused on slowing the progression of moderate CKD. Indeed, in the MDRD study, patients did not have diabetes [124], whereas PLADO can be nondifferentially prescribed to both patients with and without diabetes with any degree of severity of CKD, consistent with the broader unmet need in the adult CKD population. It is important to note that polycystic kidney disease patients, who usually have slower CKD progression rates, comprised 24% of the MDRD study participants [124].

Role of dietitians in PLADO

The successful implementation of plant-based restricted protein diets is dependent on the engagement of dietitians who are well trained in the field of nondialysis CKD [125]. Dietitians should assess regularly the dietary protein and energy as well as micronutrient intakes of CKD patients by both periodic dietary assessments and 24-hour urine collections to estimate dietary intakes of macro- and micronutrients and to evaluate and improve adherence to dietary recommendations [1]. Behavior change counseling by dietitians is a key skill set that is critical in successful lifestyle and habit modifications. Easy-to-use telehealth alternatives are important to overcome existing and emerging challenges in dietetic education, including under the COVID-19 pandemic and other restrictions, so that patients are provided with pragmatic tools and comprehensible and consistent dietary information and skills, which fosters ownership and self-monitoring in kidney health management such as healthy kitchen approaches [126,127].

Unfortunately, however, an overwhelming majority of CKD patients never meet with a CKD-specialized dietitian prior to dialysis initiation, and most patients remain uninformed about the role of diet in disease progression and management. Among clinicians and patients, lack of awareness about the benefits of plant-dominant, low-protein dietary interventions (other than low-potassium diets) and available insurance reimbursement for medical nutrition therapy under the guidance of a registered dietitian are significant barriers. In many regions, especially in North America and Europe, the focus and expertise of the dietitians have traditionally been centered on dialysis patient care as opposed to preventative nondialysis-dependent CKD. Past and recent reports suggest underutilization of dietetic manpower and expertise for the purpose of nondialysis CKD care [74]. A collective groundswell of events has recently occurred which aims to improve CKD care: the World Kidney Day focuses on the reduction of the onset and progression of CKD through primary, secondary, and tertiary measures [128]; the US Presidential Executive Order, "Advancing American Kidney Health" [129], refocuses on kidney care from dialysis incentives to avoidance of kidney failure; the US Veterans Health Administration issued Directive 1053, "Chronic Kidney Disease: Prevention, Early Recognition, and Management," establishing federal policy targeting CKD prevention through integrated care, including medical nutrition therapy [130], and, the advocacy of renal dietitians for patient-centric LPD regimens containing fewer animal products and more plant-based sources of protein such as PLADO [131]. This is a sharp contrast to prior LPD recommendations with less flexible regimens such as strict plant-based dieting or very low DPI of <0.4 g/kg/d combined with supplements, which may be less palatable, unsustainable, and nonpragmatic for broad application in the real-world scenarios of CKD patient care.

Recommendations for practical implementation of PLADO

After the first 3 months, which includes preliminary education on LPD regimens with >50% plant sources and acquiring food preparation skills, participating CKD patients should be assessed every 3–6 months by the dietitian. During each visit, dietary reeducation along with dietary assessment should be conducted and patient's progress in reaching the goals should be examined. In line with the pragmatic nature of PLADO regimens, the dietary reeducation and follow-up visits can be performed in parallel with routine follow-up CKD clinic visits on the same days of the ambulatory clinic appointments, thus avoiding the burden of additional diet-related travels to the CKD clinic. In addition to in-person visits, there could be monthly to trimonthly telephone calls with the CKD patients under CKD therapy, or even more frequently if needed, to reinforce diet planning and adherence and to answer questions about the preparation of plant-dominant meals and cooking questions. Adherence to PLADO should be evaluated by comparing the LPD goals, that is, 0.6–0.8 g/kg/d and >50% plant sources, to the estimated DPI (eDPI) using 24-hour urine nitrogen (see later) and 3-day diet assessments, respectively. Complementary dietary education of the patients and their care partners should be provided both during the face-to-face visits and via phone calls.

The specialized knowledge and services of a renal dietitian ensure accurate nutrition education, meal planning, and evaluation of body composition to sustain health. Components of a CKD nutrition evaluation may include the following (see Table 29.5): (1) dietary education for LPD with >50% plant-based protein sources; (2) dietary assessment using a 3-day diet diary with interview; (3) simplified anthropometry that includes triceps and biceps skinfolds [132] and mid-arm circumference [133]; (4) body fat estimation using either bioimpedance analyses or near-infra red interactance [134–136]; (5) the malnutrition-inflammation score, also known as Kalantar score [137–140], including subjective global assessment [141]; and (6) handgrip strength test [142]. The dietary education along with the previous evaluations usually takes 30 minutes to 1 hour of the dietitian's time during each visit according to our previous and ongoing nutritional clinic operations.

Concurrent pharmacotherapy and other interventions

Regardless of the type of the dietary regimen, participation in the PLADO plan does not interfere with any other aspects of the CKD patient care, including prescribed medications such as angiotensin pathway modulators, other antihypertensive medications, antidiabetic medications such as SGLT2 inhibitors, phosphorus binders, potassium binders, and sodium bicarbonate. Indeed, it is expected that dietary protein restriction will have a synergistic effect on these

TABLE 29.5 Overview of the recommended ambulatory visits and tests under the plant-dominant low-protein diet (PLADO) regimen.

	Timeline of for PLADO therapy visits	**"Run-in" period**			**Year 1 (quarterly)**			**Years 2 + (semiannual)**				
	PLADO months	**0**	**1**	**3**	**6**	**9**	**12**	**18**	**24**	**30**	**36**	**Needed time**
	History and physical examination with updates on clinical and dietary status	X	x	x	x	x	X	x	x	x	x	10–20 min
Lab tests	Routine lab panel: CMP/LFT, anemia, MBD, A1c	X		x	x	x	X	x	x	x	x	<10 min
	Spot urine, urinalysis, protein, albumin, and creatinine	X		x	x	x	X	x	x	x	x	<5 min
	24 h urine: Nitrogen, Na, K, creatinine, alb, and prot.	X		x	x	x	X	x	x	x	x	Collected at home
	eGFR assessment and creatinine and urea clearance	X		x	x	x	X	x	x	x	x	
Dietitian visit	Dietary education for LPD >50% plant-based	X	x	x	x	x	X	x	x	x	X	10–20 min
	Dietary assessment, 3-day diet diary with interview	X	x	x	x	x	X	x	x	x	X	10–20 min
	Anthropometry: triceps and biceps skinfolds, mid-arm circumference[a]	X		x	x	x	X	x	x	x	X	2–4 min
	Body fat estimation[a]	X		x	x	x	X	x	x	x	X	1–2 min
	Malnutrition-inflammation score[a]	X		x	x	x	X	x	x	x	x	2–5 min
	Handgrip strength test[a]	X		x	x	x	X	x	x	x	x	1–2 min
	Phone calls to reinforce PLADO education, adherence, and meal preparation	x	x	x	x	x	X	x	x	x	x	10–30 min
Questionnaires	Diet palatability and appetite questionnaire	x	x	x	X	x	X	x	x	x	x	15–30 min
	Food frequency questionnaire[a]	x			x		X	x	x	x	x	15–30 min
	Quality of life: KDQOL including SF36 quest[a]	x		x	x	x	X	x	x	x	x	10–15 min
	Uremic symptoms questionnaire	x		x	x	x	X	x	x	x	x	10–15 min
	Self-perception and relationship questionnaire[a]	x		x	x	x	X	x	x	x	x	10–15 min

[a] *These items are more relevant to sophisticated centers or under research protocols.*

Abbreviations: *alb*, Albumin; *CMP*, comprehensive metabolic panel; *eGFR*, estimated glomerular filtration rate; *K*, potassium, Na, K, creatinine; *KDQOL*, Kidney disease quality of life; *LFT*, liver function tests; *LPD*, low-protein diet; *MBD*, Mineral and bone disorder; *Na*, sodium; *prot.*, protein; *RD*, Registered dietitian; *SF36*, short form with 36 items of quality of life.

pharmacotherapies [76]. The inclusion of plant-based foods may necessitate a reduction in any of these medications over time as the relevant parameters improve.

Laboratory tests for nutritional management of CKD

Consistent with the pragmatic and cost-efficient nature of the PLADO regimen, all relevant laboratory tests are performed in the clinical laboratories of the respective medical centers typically as part of routine CKD care. With the exception of a semiannual serum vitamin B12 level, quarterly to semiannual laboratory tests include routine chemistry panels (including serum Na, K, CO_2, Cl, urea, creatinine, and glucose), liver function tests, hemoglobin A1c, anemia, and mineral and bone disorder (MBD) parameters, including calcium, phosphorus, and parathyroid hormone. Urinalysis and spot urine for urinary protein/albumin and creatinine should be tested, and eGFR is calculated [143]. Participating patients are instructed to collect 24-hour urine samples according to the directions that should be repeated during each ambulatory visit and/or each phone call, that is: not collecting the first urine in the morning of Day 1, collecting the first urine in the morning of Day 2 as the last collection component, and the entire micturition in-between. The 24-hour urine should include measurements of urine urea nitrogen (UUN), sodium (UNa), potassium UK, creatinine (UCr), albumin, and protein, as well as urine volume (UV). The following measures should be calculated and reviewed by both the nephrologist and dietitian during each visit [1] (Fig. 29.5):

1. Creatinine clearance: **UCr*UV/SCr** in mL/min, and to compare to eGFR.

2. Creatinine index: **UCr/weight (mg/kg)**, to identify 24-hour urine collection inaccuracies, including under- and overcollections by comparing it to the expected value of 1–2 mg/kg/d for women and 1.5–2.5 mg/kg/d for men.
3. eDPI: **UUN*6.25 + 0.03*weight** (g/kg/d); for patients with substantial proteinuria >3 g/d, the daily proteinuria amount is added to the eDPI [1,74].
4. Estimated dietary Na intake: **UNa in mmol/44** (g/d).
5. Estimated dietary K intake: **UK in mmol/25** (g/d).
6. 24-hour urinary protein and albumin excretion (mg/d).

See Table 29.5 for the overview of the laboratory tests.

Suggested self-administered questionnaires

Based on the goals and the extent of the operation and resources of the CKD clinic, some to all of the following self-administered questionnaires can be used during each or alternating ambulatory visit: (1) diet, palatability, and appetite questionnaire: the appetite component allows grading appetite and recent changes [144]. The palatability component includes 12 items and grades palatability and feasibility of dietary intervention [144]. These items are combined with the diet assessment of the HEMO study [145]. (2) Quality of life KDQOL, including SF36: This has been used and validated

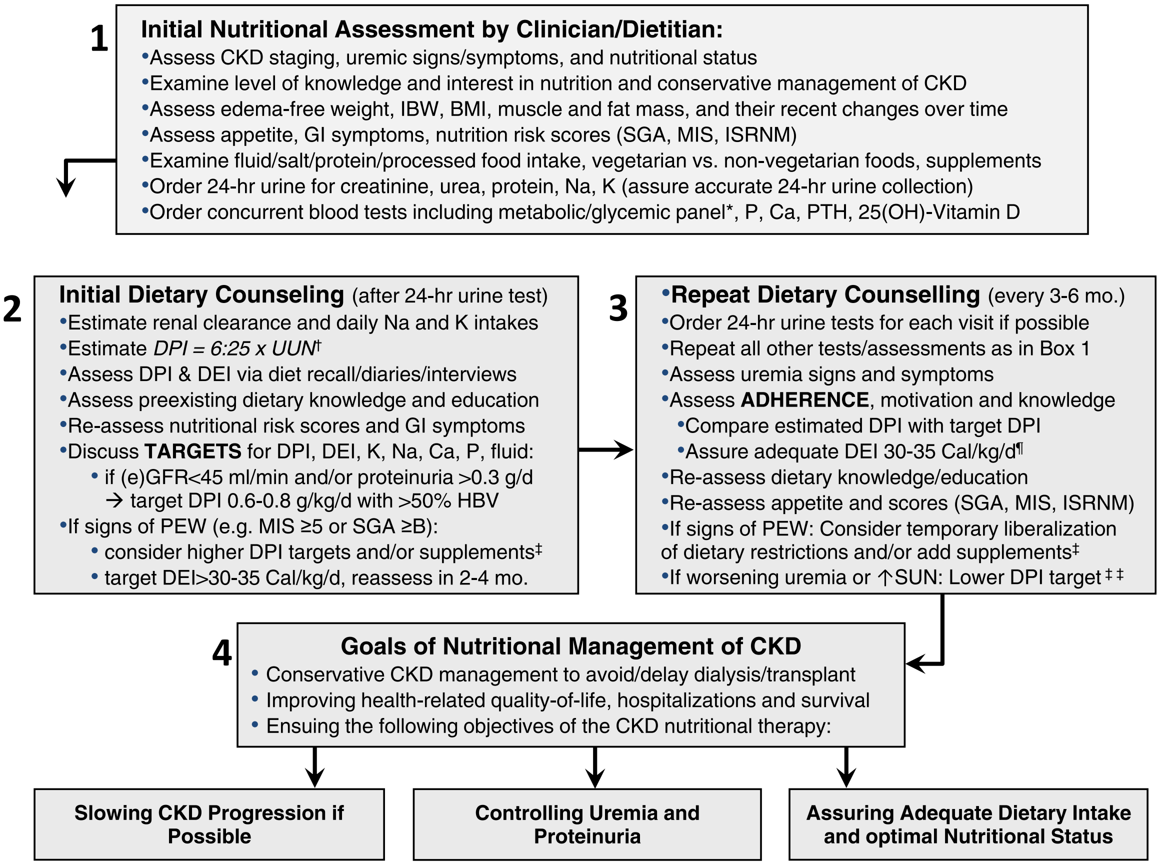
1
Initial Nutritional Assessment by Clinician/Dietitian:
•Assess CKD staging, uremic signs/symptoms, and nutritional status
•Examine level of knowledge and interest in nutrition and conservative management of CKD
•Assess edema-free weight, IBW, BMI, muscle and fat mass, and their recent changes over time
•Assess appetite, GI symptoms, nutrition risk scores (SGA, MIS, ISRNM)
•Examine fluid/salt/protein/processed food intake, vegetarian vs. non-vegetarian foods, supplements
•Order 24-hr urine for creatinine, urea, protein, Na, K (assure accurate 24-hr urine collection)
•Order concurrent blood tests including metabolic/glycemic panel*, P, Ca, PTH, 25(OH)-Vitamin D
2
Initial Dietary Counseling (after 24-hr urine test)
•Estimate renal clearance and daily Na and K intakes
•Estimate DPI = 6:25 x UUN†
•Assess DPI & DEI via diet recall/diaries/interviews
•Assess preexisting dietary knowledge and education
•Re-assess nutritional risk scores and GI symptoms
•Discuss TARGETS for DPI, DEI, K, Na, Ca, P, fluid:
• if (e)GFR<45 ml/min and/or proteinuria >0.3 g/d → target DPI 0.6-0.8 g/kg/d with >50% HBV
•If signs of PEW (e.g. MIS ≥5 or SGA ≥B):
• consider higher DPI targets and/or supplements‡
• target DEI>30-35 Cal/kg/d, reassess in 2-4 mo.
3
•Repeat Dietary Counselling (every 3-6 mo.)
•Order 24-hr urine tests for each visit if possible
•Repeat all other tests/assessments as in Box 1
•Assess uremia signs and symptoms
•Assess ADHERENCE, motivation and knowledge
•Compare estimated DPI with target DPI
•Assure adequate DEI 30-35 Cal/kg/d¶
•Re-assess dietary knowledge/education
•Re-assess appetite and scores (SGA, MIS, ISRNM)
•If signs of PEW: Consider temporary liberalization of dietary restrictions and/or add supplements‡
•If worsening uremia or ↑SUN: Lower DPI target‡‡
4
Goals of Nutritional Management of CKD
• Conservative CKD management to avoid/delay dialysis/transplant
• Improving health-related quality-of-life, hospitalizations and survival
• Ensuring the following objectives of the CKD nutritional therapy:
Slowing CKD Progression if Possible
Controlling Uremia and Proteinuria
Assuring Adequate Dietary Intake and optimal Nutritional Status

FIGURE 29.5 *Proposed algorithm and steps for the approach to the nutritional management of patients with chronic kidney disease.* *Comprehensive metabolic and glycemic panels include electrolytes, SUN, creatinine, glucose, A1c, liver function tests, and the lipid panel. †The full equation is: $DPI = 6.25XUUN\ +\ 0.03 \times IBW$. Add the amount of daily proteinuria in grams if proteinuria >5 g/d. Calculate the *creatinine index* (24-h urine creatinine divided by actual weight or IBW if obese) and compare it to the expected value of 1–1.5 g/kg/d for women and 1.5–2 g/kg/d for men. ‡Dietary supplements can be added to provide additional sources of energy and/or protein, including—but not limited to—CKD-specific supplements, essential amino acids, or keto-analogs (ketoacids) of amino acids. ¶To ensure adequate DEI of at least 30–25 Cal/kg/d, higher fat intake can be considered, for example, unsaturated fats, omega 3–rich flaxseed, canola, and olive oil. ‡‡If worsening uremic signs and symptoms occur, DPI <0.6 g/kg/d with or without supplements can be considered. *BMI*, Body mass index; *CKD*, chronic kidney disease; *d*, day; *DEI*, dietary energy intake; *DPI*, dietary protein intake; *eGFR*, estimated glomerular filtration rate; *GI*, gastrointestinal; *HBV*, high biologic value; *IBW*, ideal body weight; *ISRNM*, International Society of Renal Nutrition and Metabolism; *K*, potassium; *MIS*, malnutrition-inflammation score; *Na*, sodium; *PEW*, protein-energy wasting; *Phos.*, phosphorus; *PTH*, parathyroid hormone; *SGA*, subjective global assessment; *SUN*, serum urea nitrogen; *UUN*, urine urea nitrogen. Source*: Adapted from Kalantar-Zadeh K, Joshi S, Schlueter R, Cooke J, Brown-Tortorici A, Donnelly M, et al. Plant-dominant low-protein diet for conservative management of chronic kidney disease. Nutrients 2020;12(7). https://doi.org/10.3390/nu12071931. PubMed PMID: 32610641; PMCID: PMC7400005. https://www.ncbi.nlm.nih.gov/pubmed/32610641.*

extensively [139]. (3) Uremic symptoms questionnaire: This questionnaire is derived from the "Symptom Assessment Instrument" by Weisbord et al. [146], which was created and validated in US veterans with stage 5 CKD. (4) Self-perception and relationship questionnaire: This item will assess the psychosocial—spiritual well-being using the 28-item scale [147]. (5) Food frequency questionnaire (FFQ) [148]: This questionnaire has been developed by Kalantar-Zadeh et al. using the Block FFQ from UC Berkeley and can be used semiannually to annually (see Table 29.5).

Diet safety and transient dietary regimen suspension

Once a patient has completed the 3-month run-in period, including dietary education and food preparation training and adjustments, there should be periodic (every 3—6 months) ambulatory visits with continued data collection and review. If PEW signs are observed, or in the case of an event that requires suspension of the LPD such as hospitalization with AKI, regardless of dialysis need, or major adverse cardiovascular events, the LPD can be transiently suspended, and the patient can resume the LPD and the study protocol at a later time, usually within 90 days of the suspension of the dietary regimen participation if deemed safe. Serum potassium levels >5.5 mEq/L will preferentially be managed by potassium binders (first line) and/or reducing the potassium-rich components of the diet (second line), as opposed to the current standard of care in that traditional low-potassium dietary adjustments are pursued as the main approach, followed as needed by the administration of potassium binders.

Challenges and pitfalls of the dietary management of CKD

As stated earlier, the proposed plant-dominant diet may cause hyperkalemia and could, thus, be hazardous to patients with advanced CKD. Nephrologists and dietitians should closely monitor patients during the 3-month run-in period and thereafter for adverse events. Dietitian support is necessary for appropriate education on culinary strategies to reduce excessive potassium content while preserving flavor and nutrition. Physicians should take appropriate actions, including the use of potassium binders or suspension of the patient's participation, if this should be the safest approach. We do not expect that most patients on plant-based diets will develop hyperkalemia, as these diets are alkalinizing and alter intestinal transit time (see earlier), especially if dried fruit, juices, smoothies, and sauces can be minimized or avoided along with judicious avoidance of processed food with added potassium-based additives and preservatives [100]. Those who are extremely prone to develop hyperkalemia would display this early in the course of the intervention and the PLADO would be discontinued if hyperkalemia cannot be controlled. Less constipation as a result of PLADO is associated with favorable CV and renal outcomes [149,150].

It is important to note that the emerging standard of care in CKD is a restricted protein diet of 0.55—0.6 g/kg/d for nondiabetic CD and 0.6—0.8 g/kg/d for diabetic CKD according to the updated kidney disease outcomes quality initiative (KDOQI) nutrition guidelines as of September 2020 [151], and if this is implemented, this is in support of our PLADO regimen. Whereas it is true that an LPD should be the stated goal according to the 2020 KDOQI guidelines, this is typically not followed in everyday clinical practice, where dietary interventions are driven by biochemical abnormalities such as hyperkalemia or hyperphosphatemia. Indeed, prior KDOQI guidelines had recommended DPI of 0.8 g/kg/d without any clear range, which is rarely pursued in a real-world scenario.

It could be argued that under the PLADO regimen, there is no clear meal plan. However, this indeed ensures the intended flexibility and pragmatism of the PLADO regimen. The patient and the dietitian should work together in establishing a patient specific "Healthy Kitchen for CKD" and patients and their care partner should gain experience in implementing patient-centered dietary interventions for CKD management. Careful and balanced industry partnership can be sought to develop innovative "Healthy Kidney Diet Plans" to help people with CKD change their diet to delay the progression of the disease and to defer and prevent kidney failure.

It has been argued that many people with CKD enjoy eating high amounts of meat, and it is highly unlikely that they will adopt an LPD with >50% plant sources, especially since many dietitians recommend a high-protein diet as an approach against obesity and diabetes. Several authors of this review chapter, including both nephrologists and dietitians, have successfully implemented an LPD and plant-dominant diet education in CKD in their respective medical centers. They are aware of the cultural and dietary challenges, including in Americans and other Westerners as described in their published reports [74], and have been able to introduce and implement the PLADO regimens as described here.

Another potential challenge is the misconception related to the definition of the conservative management of advanced CKD, which is often confused with palliative and supportive care toward the end of life and without requiring special diets. This incorrect assumption is the result of confusing different types of conservative management of CKD, and their similarities and distinctions that have recently been better clarified [152], in that a dietary approach, including PLADO, is a "preservative" management of CKD and a life-sustaining and kidney rejuvenating alternative.

To summarize the last several sections of this chapter, plant-based foods and plant-dominant recipes and meal plans have been identified as a fundamental dietary component for health among a wide variety of eating patterns. Plant-based diets are an umbrella term used to describe eating patterns that included a large proportion of plant-dominant foods. Examples of this include flexitarian, vegetarian, Mediterranean, PLADO diet, and vegan diets (Table 29.6) [62]. Unrefined, whole-, plant-based foods are recommended over their highly processed forms. The consumption of whole-, plant-based foods has been shown to be useful in the prevention and treatment of many of the lifestyle-related scourges of Western societies, including T2DM, obesity, hypertension, and hyperlipidemia. In recent years, their utility for CKD and its resultant benefits and potential challenges have become increasingly apparent [62].

Dietary sodium and fluid intake

The association between dietary sodium and blood pressure is most pronounced in persons who consume high sodium (> 4 g/d), have underlying hypertension, or over age 55 years [153]. In established CKD, dietary sodium restriction is invariably recommended to control fluid retention and hypertension, and to improve CV risk profiles [154]. However, it is not clear that dietary salt restriction can slow the progression of established kidney disease. Since CV trials involving dietary sodium restriction often exclude patients with renal disease, there are limited relevant interventional data in this population [155]. Lower sodium intake enhances the effects of an LPD and angiotensin modulation therapy in decreasing intraglomerular pressure (Fig. 29.1) [156] and may decrease proteinuria and slow kidney disease progression [157]. Observational studies using urinary sodium excretion as a surrogate of salt intake have yielded inconsistent data ranging from null [158] to positive associations [159] between dietary sodium intake and renal disease progression. A recent longitudinal study using serial 24-hour urine collections in 3939 patients with CKD suggested that the highest versus lowest quartile of urinary sodium excretion (≥4.5 vs <2.7 g/d) was associated with 45% higher mortality and 54% higher risk of disease progression [159]. Incrementally worse CV outcomes were

TABLE 29.6 Examples and descriptions of various plant-based diets.

Diet type	Description
DASH diet	A specific dietary strategy designed to emulate the health-promoting effects of plant-based diet but allow for some animal-based foods, like lean meat and low-fat dairy. Modern iterations have emphasized the unprocessed forms of fruits, vegetables, legumes, and grains (as opposed to fruit juices, refined grains, etc.)
Mediterranean	Although definitions and practices vary, particularly in time and place, the Mediterranean diet typically emphasizes whole, plant foods from that area with moderate consumption of lean meats, dairy, and seafood. Added sugars, processed foods, and red meat are generally excluded but healthy fats like olive oil are included. The recently updated KDOQI nutrition guidelines give a grade 2C recommendation for the potential of Mediterranean diets to improve lipid profiles in patients with nondialysis CKD
Flexitarian	Also commonly referred to as a "semivegetarian." Represents a diet that emphasizes plant-based foods but may periodically include meat and other animal-based foods
Vegetarian	A diet that excludes meat (beef, pork, and chicken) but may include fish, dairy, or eggs and often specified as a pescatarian, lacto vegetarian, or ovo vegetarian, respectively. Combinations of these are possible
Whole-food, plant-based	A diet that emphasizes the consumption of whole-, plant-based foods as opposed to refined or processed plant foods (like potato chips or white bread) while still typically avoiding animal-based foods. It is also the diet most widely promulgated by health professionals recommending a plant-based diet
Vegan	A diet and, in some cases, a lifestyle that avoids the use of products derived from animals
PLADO	Plant-dominant, low-protein diet for patients with kidney disease: 0.6−0.8 g/kg/d dietary protein with >50% from plant-based sources, dietary sodium of <4 g/d sodium (<3 g/d if uncontrolled hypertension or edema), and dietary energy of 30−35 Cal/kg ideal body weight per day

CKD, Chronic kidney disease; *DASH*, Dietary Approaches to Stop Hypertension.

Adapted from Joshi S, McMacken M, Kalantar-Zadeh K. Plant-based diets for kidney disease: a guide for clinicians. Am J Kidney Dis 2021;77:287−96. https://doi.org/10.1053/j.ajkd.2020.10.003. PubMed PMID: 33075387. https://www.ncbi.nlm.nih.gov/pubmed/33075387.

observed when dietary sodium intake exceeded 4 g/d [160]. Recent observations in the general population suggest a J-shaped association in which both higher and lower dietary sodium intake (>5 and <3 g/d) were associated with higher risk of CV disease and death [161]. Considering these recent data and lack of evidence in kidney disease populations to support extrapolating the *RDA* of <2.3 g/d (<100 mmol/d) that is often recommended for CV disease management, we recommend a dietary sodium intake of <4 g/d (<174 mmol/d) for the overall management of CKD and its associated risks, and <3 g/d (<131 mmol/d) for specific management of symptomatic fluid retention or proteinuria. Evidence that safely supports a more stringent sodium restriction of <1.5 g/d (<87 mmol/d) given the risk of hyponatremia and adverse outcomes in renal insufficiency is lacking [162], but individualized decisions should override a generalized application of sodium restriction (Table 29.7).

Whereas adequate fluid intake may mitigate risk of kidney disease [164], patients with renal insufficiency generally have isosthenuria; thus in patients with stage 3 CKD, fluid intake should be restricted to <1.5 L per day to avoid hyponatremia [162], but adjustments of that limit for hot climate and other conditions with high insensible fluid losses are imperative. Adjunctive therapy with loop diuretics is often prescribed, particularly in patients who tend to develop symptomatic fluid retention or hyponatremia, given the association of such conditions in CKD with poor outcomes [162].

Dietary potassium

Many potassium-rich foods, such as fresh fruits and vegetables, are considered healthy choices for most people, given their higher fiber and vitamin content and lower acidogenicity [165]. In some large population cohorts at high-risk for CV disease [158] or diabetes [166], higher urinary potassium excretion is associated with lower likelihood of all renal complications except for hyperkalemia. Given the well-established association of higher dietary potassium with lower sodium intake and lower incidence of hypertension, stroke, nephrolithiasis and kidney disease, a relatively high daily potassium intake of 4.7 g/d (120 mmol/d) is recommended for healthy adults, including those at high risk of kidney disease [167]. There are, however, inconsistencies in the epidemiologic data pertaining to potassium intake in preexisting renal disease, because higher dietary potassium intake may be associated with higher risk of disease progression [159]. In very advanced CKD the highest versus lowest quartile of dietary potassium intake is associated with a 2.4-fold higher death risk independent of serum potassium level and other nutritional parameters [168]. In epidemiologic studies, both moderately low (<4.0 mmol/L) and high (>5.5 mmol/L) serum potassium levels are associated with faster kidney disease progression [169]. In hyperkalemic patients, especially in those with more advanced stages of kidney disease, dietary potassium restriction is often recommended to avoid hyperkalemia. However, excessive dietary restrictions expose patients to less heart-healthy and more atherogenic diets [170], and worsen constipation, which may result in higher gut potassium absorption [94]. Despite a higher predilection for hyperkalemia with progression of kidney disease, few studies have examined the effects of dietary potassium restriction, or methods of extracting potassium during food preparation and cooking. It is not clear whether potassium-binding agents can allow the liberalization of dietary potassium intake with the inclusion of healthier potassium-rich food items [165]. In patients with a tendency toward hyperkalemia (>5.5 mEq/L), a dietary potassium restriction of <3 g/d (<77 mmol/d) is recommended, with the stipulation that a balanced intake of fresh fruits and vegetables with high fiber should not be compromised (Table 29.7).

Dietary phosphorus

In the general population, higher plasma phosphorus levels have been associated with an increased risk of incident kidney disease [171]. Overt hyperphosphatemia is infrequent in stages 1–3 of CKD, given the heightened expression and release of parathyroid hormone and FGF-23 in renal insufficiency, which promote urinary phosphorus excretion [172]. However, elevated PTH and FGF-23 can cause renal bone disease, left ventricular hypertrophy, vascular calcification, and accelerated kidney disease progression from vascular and tubulointerstitial injury (Fig. 29.2), highlighting the importance of dietary phosphorus management even without apparent hyperphosphatemia [173]. While an LPD also decreases phosphorus intake, different proteins contain varying quantities and bioavailability of phosphorus; for instance the phosphorus-to-protein ratio of egg whites and egg yolks are 1–2 and 20–30 mg/g, respectively [174]. The gut absorption of plant phosphorus and fibers, mostly in the form of phytates, is less than meat (30%–50% vs 50%–70%, respectively) [82]. As food additives include readily absorbable inorganic phosphorus (up to 100%), ingesting processed foods causes an even higher phosphorus burden [175]. A dietary phosphorus restriction to <800 mg/d is recommended among patients with moderate-to-advanced kidney disease, and processed

TABLE 29.7 Recommended dietary and nutrient intake for different stages of kidney disease in adults.

	Normal kidney function (eGFR >60[a]) and no proteinuria, but at higher CKD risk, for example, diabetes, hypertension, or solitary kidney[b]	**Mild-to-moderate CKD (eGFR 30−<60[a]) without substantial proteinuria (<0.3 g/d)[c]**	**Advanced CKD (eGFR <30[a]) or any CKD with substantial proteinuria (>0.3 g/d)[c]**	**Transitioning to dialysis therapy with good RKF, including incremental dialysis preparation[c]**	**Prevalent dialysis therapy, or any CKD stage with existing or imminent PEW[d]**
Dietary protein (g/kg/d based on IBW)[e]	<1.0 g/kg/d, increase proportion of plant-based proteins	<1.0 g/kg/d (consider 0.6−0.8 if eGFR <45 mL/min 1.73 m^2 and fast progression)	0.6−0.8 g/kg/d, including 50% HBV, or <0.6 g/kg/d with addition of EAA/KA	0.6−0.8 g/kg/d on nondialysis days (e.g., incremental dialysis) and >1.0 g/kg/d on dialysis days	1.0−1.2 g/kg/d, may require >1.5 g/kg/d if hypercatabolic
Dietary sodium (g/d)	<4 g/d (<3 g/d for HTN)[f]	<4 g/d, avoid <1.5 g/d if hyponatremia likely	<3 g/d, avoid <1.5 g/d given high likelihood of hyponatremia	<3 g/d	<3−4 g/d
Dietary potassium (g/d)	Same as recommended for the general population (4.7 g/d)	Same as the general population unless frequent or severe hyperkalemia excursions likely	<3 g/d if hyperkalemia occurs frequently while maintaining high fiber intake	<3 g/d if hyperkalemia occurs frequently while maintaining high fiber intake	<3 g/d[g], target high fiber intake (see under fibers)
Dietary phosphorus (mg/d)[h]	<1000, minimize added inorganic P in preservatives and processed foods	<800, minimize added inorganic P, encourage more vegetarian food (see next)	<800, minimize added inorganic P, more vegetarian food (see next)	<800, minimize added inorganic P. Consider P binder therapy	<800, minimize added inorganic P. Add P binders as needed
Dietary calcium (mg/d)	1000−1300 mg/d (to be adjusted for age)	800−1000 mg/d	800−1000 mg/d	800−1000 mg/d or less	<800 mg/d
Fibers, alkali, and vegetarian foods	25−30 g/d, target higher proportion (>50%) of plant-based foods such as DASH diet	25−30 g/d or more, higher proportion (>50%) of plant based foods	25−30 g/d or higher, consider >70% vegetarian foods	25−30 g/d or higher	25−30 g/d or higher, suggest avoiding strict vegan dieting
Energy[i] (Cal/kg/d)	30−35 Cal/kg/d[j] adjust to target weight reduction if BMI >25 kg/m^2	30−35 Cal/kg/d, increase proportion with LPD	30−35 Cal/kg/d, increase proportion with LPD	30−35 Cal/kg/d	30−35 Cal/kg/d, target higher if PEW exists or imminent
Fats	Mostly mono- and poly-unsaturated lipids, including omega 3 fatty acids	Mostly mono- and poly-unsaturated lipids, including omega 3 fatty acids, increase proportion with LPD	Mostly mono- and poly-unsaturated lipid, including omega 3 fatty acids, increase proportion with LPD	Mostly mono- and poly-unsaturated lipid, including omega 3 fatty acids	Mostly mono- and poly-unsaturated lipid, including omega 3 fatty acids
Vitamin D	Nutritional D (ergo- or cholecalciferol) as needed	Nutritional D or calcifediol, consider adding 1α-OH D analogs in progressive sHPT	Nutritional D or calcifediol, add 1α-OH D analogs in progressive or symptomatic sHPT	1α-OH D analogs to control sHPT	1α-OH D analogs to control sHPT, add calcimimetics as needed
Other vitamins and trace elements	Recommend daily multivitamin intake	Avoid aluminum-based medications, monitor iron indices, and ensure iron therapy as needed	Avoid aluminum and magnesium-based agents. Treat iron deficiency	Avoid aluminum, and magnesium-based agents. Treat iron deficiency	Avoid aluminum and magnesium-based agents. Treat iron deficiency
Management of weight	Lipid and weight reduction strategies target BMI in	Avoid excessive weight loss, consider	Identify unintentional weight	Identify unintentional	Avoid weight loss or BMI <23 kg/m^2 unless

(*Continued*)

TABLE 29.7 (Continued)

	Normal kidney function (eGFR >60[a]) and no proteinuria, but at higher CKD risk, for example, diabetes, hypertension, or solitary kidney[b]	Mild-to-moderate CKD (eGFR 30− < 60[a]) without substantial proteinuria (<0.3 g/d)[c]	Advanced CKD (eGFR <30[a]) or any CKD with substantial proteinuria (> 0.3 g/d)[c]	Transitioning to dialysis therapy with good RKF, including incremental dialysis preparation[c]	Prevalent dialysis therapy, or any CKD stage with existing or imminent PEW[d]
and cardio-vascular risks	18.5–25 kg/m^2 range, recommend regular exercise training	careful exercise training, follow conventional lipid targets	loss and intervene with higher energy and protein	weight loss and intervene with higher energy and protein	required for imminent kidney transplantation or other life-saving interventions
Fluid management	No fluid restriction, adequate hydration >1.5 L/d (if risk of hyponatremia is minimal)	<1.5 L/d if edematous state or hyponatremia, consider adding diuretics	<1.5 L/d[k], consider loop diuretics and titrate the dose or sliding scale dosing[l]	<1.5 L/d[k], consider more frequent high-dose loop diuretics	<1 L/d, avoid excessive ultrafiltration on dialysis

[a] *The unit for eGFR is mL/min/1.73 m^2 BSA.*

[b] *Solitary kidney can be congenital, acquired, or surgical, including status postdonor or cancer nephrectomy.*

[c] *Prevalent renal transplant recipients are often in the two categories of eGFR 30− < 60 and >30 mL/min/1.73 m^2, or transitioning to dialysis and can be approached similarly.*

[d] *PEW according to the International Society of Renal Nutrition and Metabolism criteria [163].*

[e] *The IBW is to be used for kg in the denominator of all dietary recommendations especially in persons with a BMI >30 kg/m^2. IBW can be estimated in kg in males (=50 + 2.3 kg for each inch over 5 ft) and females (=45.5 + 2.3 kg for each inch over 5 ft).*

[f] *In patients with heart failure the recommendations of the American Heart Association (http://www.heart.org) can be considered. The American Heart Association recommends no more than 2.3 g/d (equivalent of a teaspoon salt) and suggests an ideal limit of no more than 1.5 g/d (source: https://sodiumbreakup.heart.org).*

[g] *In hypokalemic peritoneal dialysis patients, higher potassium intake should be targeted.*

[h] *Dietary phosphorus restriction is independent of hyperphosphatemia.*

[i] *Carbohydrates provide 40%–60% of the daily energy intake, should be natural (unrefined) and complex with high fiber content (see under fibers).*

[j] *In obese patients, lower energy ranges can be targeted.*

[k] *In the case of worsening edema, more stringent fluid restrictions may be necessary such as <1 L/d.*

[l] *Sliding scale dosing of loop diuretics instructs upward dosing for fluid retention and downward dosing for volume depletion based on daily weight and other parameters.*

1α-OH D, 1-alpha-hydroxylted vitamin D; *BMI*, body mass index; *BSA*, body surface area; *Cal*, kilo-calorie; *CKD*, chronic kidney disease; *d*, per day (such as in g/kg/d); *D*, vitamin D; *DASH*, Dietary Approaches to Stop Hypertension; *DPI*, dietary protein intake; *EAA*, essential amino acids; *eGFR*, estimated glomerular filtration rate in mL/min/1.73 m^2 BSA; *HBV*, high biologic value protein; *HTN*, hypertension; *IBW*, ideal body weight; *KA*, ketoacids (keto-analogs of amino acids); *LPD*, low-protein diet; *P*, phosphorus; *PD*, peritoneal dialysis; *PEW*, protein-energy wasting; *RKF*, residual kidney function; *sHPT*, secondary hyperparathyroidism.

foods with a higher phosphorus-to-protein ratio should be minimized. However, in patients transitioning to dialysis or who are at higher risk of PEW, restricting protein intake to control hyperphosphatemia may be associated with worse outcomes [176]. Thus an individualized dietary approach that incorporates ample use of phosphorus binders is warranted [177].

Dietary calcium and vitamin D

The renal insufficiency-associated decline in 1,25 $(OH)_2$ vitamin D diminishes GI absorption of calcium; however, passive diffusion of ionized calcium continues and may lead to a positive calcium balance, aggravated by diminished urinary calcium excretion from secondary hyperparathyroidism [178]. Higher calcium release from bone in hyperactive renal bone disease enhances positive calcium balance and worsens vascular calcification [179]. Gut calcium absorption varies given differential dissociation and bioavailability of elemental calcium type; for instance calcium citrate is more readily absorbable than calcium acetate [178]. Two recent balance studies suggested that an intake of 800–1000 mg/d of elemental calcium can achieve stable calcium balance in people with stages 3–4 CKD [178,180]. Hence, whereas the suggested calcium intake for persons without kidney disease is 1000–1300 mg/d [178], in moderate-to-advanced CKD 800–1000 mg/d of elemental calcium from all sources should suffice (Table 29.7) [178,180].

Nutritional vitamin D (cholecalciferol or ergocalciferol) may be offered to patients with kidney disease, whose circulating vitamin D levels are documented as low. In some studies, vitamin D analogs have been associated with decreased proteinuria in addition to the healing of renal osteodystrophy [181]. Notwithstanding inconsistent data about the requirement for and effect of vitamin D in certain CKD subpopulations, including inherently lower vitamin D and higher parathyroid hormone levels in African-Americans [182], 1-alpha-hydroxated vitamin D agents or, calcifediol may be needed in addition to nutritional vitamin D to control progressive secondary hyperparathyroidism [183].

Vegetarian diet, fibers, and the microbiome

Data from populations with largely vegetarian-based diets do not clearly distinguish a differential risk of plant- versus animal-based protein on the future likelihood of kidney disease [184]. Plant foods are recommended as part of many kidney disease prevention and management strategies, since these contain less saturated fatty acids, protein, and absorbable phosphorus and generate less acid and are rich in fibers, poly- and mono-unsaturated fatty acids, magnesium, potassium, and iron. In CKD a diet with a higher proportion ($>50\%-70\%$) of plant sources is associated with better patient outcomes [71]. Constipation can lead to higher retention of uremic toxins and hyperkalemia, whereas loose stools may enhance fluid loss and removal of nitrogenous products [150]. The protein in a vegetarian diet is less fermentable and has high fiber content, increasing peristalsis and bowel movements, and is associated with less production, exposure, and absorption of uremic toxins [185].

Uremia per se as well as dietary restrictions and pharmacotherapy, including antibiotics, may alter gut microbiome, and this may have a bearing on kidney disease symptoms and progression [186]. Microbiome modulation by dietary interventions such as probiotics may offer an opportunity to control production, degradation, and absorption of certain uremic toxins that are fermentation by-products of the gut microbial activities, including indoxyl sulfate, *p*-cresol, and trimethylamine [186]. Nutritional and pharmacologic approaches, including the use of ingestible absorbents and high fiber or vegetarian diets, are tested as a means to reduce gut absorption of uremic toxins to control uremic symptoms and to slow disease progression [187].

Carbohydrates, fats, and dietary energy

When unrefined, carbohydrates comprise 40%–60% of the daily energy intake, and even higher with an LPD. Carbohydrates should be complexed with high fiber content to help reduce dietary phosphorus and protein, urea, and creatinine generation [86]. Such a diet also promotes a more favorable microbiome [188] with less constipation [150]. Unsaturated fat is the preferred lipid in the diet. Butter should be replaced by omega-3-rich flaxseed, canola, or olive oil [170]. A recent study suggested that dietary omega-3 fatty acid supplementation in diabetic patients with hypertriglyceridemia may reduce albuminuria and preserve renal function [189]. There is currently no evidence demonstrating that low-fat diets, recommended by some guidelines, improve kidney disease outcomes. In an LPD, fat and carbohydrate should altogether comprise $>90\%$ of the daily energy intake requirement of 30–35 Cal/kg/d to avoid PEW [26]. Whereas in patients with diabetic kidney disease proper glycemic control should be maintained, adequate energy intake is needed to mitigate the risk of PEW and hypoglycemia that may occur more frequently with worsening kidney function.

Dietary management of acidosis in kidney disease

Daily acid production results from bicarbonate losses in the gut (20–30 mEq/day), breakdown of amino and nucleic acids from proteins (20–30 mEq/day), and oxidation of carbohydrates and fats to lactic and ketoacids (10–20 mEq/day) [190]. The kidneys regenerate the bicarbonate used for buffering by the excretion of both net acid and acid buffers, including phosphate, and by ammoniagenesis through deamination of glutamine in the proximal tubule and its titration to ammonium in the collecting ducts with subsequent urinary excretion (Fig. 29.2) [190]. Hence, kidney disorders, including associated renal tubular defects, are often associated with chronic metabolic acidosis, which leads to glucocorticoid overproduction with resultant muscle wasting, worsens uremia-associated insulin resistance, and increases parathyroid hormone release [191]. Metabolic acidosis is associated with more rapid kidney disease progression and poorer survival. Hyperparathyroidism along with chronic buffering of acid by bone leads to a progressive loss of bone mineral and worsening renal osteodystrophy. Hence, reduced protein intake with a greater proportion of diet from vegetarian sources to correct acidosis improves bone mineralization and may slow protein breakdown and disease progression [192]. Adjunctive alkali therapy can also be considered to mitigate acidosis in CKD [193].

Trace elements and vitamins

Patients with kidney disease often suffer from an imbalance of several critical trace elements and vitamins. Inadequate food intake may result in insufficient ingestion of antioxidant vitamins, including vitamins C and E and carotenoids, and with more advanced renal disease, vitamin deficiencies for folate, vitamin K, and calcitriol ensue [194]. Micronutrient imbalance in kidney disease may contribute to a higher burden of oxidative stress, inflammation, and CV disease [194,195]. Among the trace elements, iron deficiency is most problematic, given the high frequency of GI blood losses in CKD [196]. Deficiencies of zinc, copper, and selenium may occur; in contrast, toxicities are more common with aluminum, magnesium, and possibly cadmium [194]. A recent study showed that 800 mcg/d of folic acid added to enalapril led to slower disease progression than enalapril alone [197]. Vitamin K supplementation may blunt the development of vascular calcification based on experimental models of CKD [198]. Daily intake of other vitamins and trace elements at conventional doses is often recommended both for persons at high risk for kidney disease and for those with established renal insufficiency (see additional references with comprehensive data on vitamins and trace elements in kidney disease) [194,195].

Management of weight and CV risk

Evidence suggests that obesity, that is, body mass index $>30\ \mathrm{kg/m^2}$, is associated with a higher lifetime risk of kidney disease [199]. In a recent study in over three million US veterans without prior kidney disease, obese men exhibited a more rapid decline in kidney function over time [200]. Conventional lipid and weight reduction strategies are recommended for persons at higher risk of kidney disease, including those who underwent a nephrectomy. Regular exercise training and general population targets for weight and CV risk reduction can be especially pursued in earlier stages of CKD [201]. Patients with hypertension are often recommended to follow an energy-controlled "Dietary Approaches to Stop Hypertension" diet, that is high in fruit, vegetables, whole grains, and low-fat dairy products and low in saturated fat, cholesterol, refined grains, sweets, and meat, and which may help with weight reduction in obesity [202]. The efficacy and safety of bariatric surgery to mitigate the risk of kidney disease are unclear [203]. A decrease in GFR has been observed after bariatric surgery, possibly because hyperfiltration is reduced; hence, the observation may have favorable implications [204]. Nevertheless, in more advanced CKD, greater longevity has been paradoxically reported with larger body size, which may reflect a more resilient nutritional profile. Hence, any unintentional edema-free weight loss warrants timely workup and dietary interventions, and unnecessary weight loss in advanced kidney disease should be avoided, unless absolutely required for an imminent kidney transplantation or other life-saving procedures [205].

Conclusion and practice strategies

Given the high incidence and prevalence of CKD and urgent need for alternative disease management strategies, nutritional interventions with disease-specific dietary ranges (Table 29.7) are safe, patient-centered, and cost-effective interventions that may help provide greater longevity and longer dialysis-free interval to millions of people worldwide. Dietary protein, energy, and micronutrient intakes should be assessed regularly by both dietary assessments and 24-hour urine collections to evaluate and improve adherence, while excessive restrictions may be harmful and should be avoided. Additional studies are needed to fill existing knowledge gaps and to assure a more robust evidence-based approach in the nutritional management of CKD.

Conflicts of interest

KKZ has received honoraria and/or support from Abbott, AbbVie, Alexion, Amgen, Astra-Zeneca, AVEO Oncology, Baxter, Chugai, DaVita, Fresenius, Genentech, Haymarket Media, Hospira, Kabi, Keryx, Novartis, Pfizer, Relypsa, Resverlogix, Sandoz, Sanofi, Shire, Vifor, UpToDate, and ZS-Pharma. SSJ has received honorarium from Insyght Interactive. Other coauthors have declared no conflict.

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CHAPTER

30

Use of dietary therapy in far-advanced chronic kidney disease to delay renal replacement therapy or facilitate incremental dialysis transition

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Introduction

Patients with chronic kidney disease (CKD) manifest a wide range of metabolic derangements. These can either be attributed to the primary functions of the kidneys or the secondary abnormalities due to the uremic milieu. The kidneys excrete solutes and water and the deterioration of kidney function may lead to the accumulation of water and solutes, including nitrogenous-waste products, sodium, nonvolatile acids, phosphate, potassium, or other uremic toxins such as indoxyl-sulfate or *p*-cresol. The functions of kidney as an endocrine organ can deteriorate during the progression of CKD. This may be secondary to the uremic condition. On the other hand, the accumulation of uremic toxins or other factors relating to the uremic milieu alters multiple metabolic pathways [1]. Derangements in protein and energy metabolism, chronic inflammation, oxidative stress, and hormonal dysfunction ensue due to the uremic condition. The accumulation of phosphorus also affects parathyroid hormone (PTH) and fibroblast growth factor 23 (FGF23), and increased serum levels of PTH and FGF23 and deficiency of 1,25-dihydroxycholecalciferol and, not uncommonly, 25-hydroxycholecalciferol are present. These humoral factors are the key effectors in CKD−mineral bone disorders. Other hormonal abnormalities include the decrease in the secretion and the actions of growth hormone. Normal growth and development may be hindered in children [2]. The accumulation of nitrogen-containing products from dietary and endogenous protein catabolism may affect taste and smell [2]. Distorted taste and smell lead to appetite loss and further deterioration of nutritional status.

Although large numbers of studies have examined dietary therapy for patients with CKD [3−5], the role of this treatment remains controversial [6]. The Center for Disease Control and Prevention (CDCP) defines the term "prevention" as the activities of three stages: primary prevention, secondary prevention, and tertiary prevention. An Expert Panel of the CDCP proposed and applied these three stages of prevention for the management of CKD [7]. Primary prevention encompasses risk factor management to prevent the development of CKD and cardiovascular disease. Secondary prevention has the goal of slowing CKD progression

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and delaying/deferring commencement of renal replacement therapy (RRT). Tertiary prevention aims to manage uremic symptoms and comorbidities.

Traditionally, two major indications for dietary therapy for patients with CKD have been proposed. One indication is to reduce damage to the kidney, thereby decreasing progressive kidney injury and scarring and reducing the rate of progressive loss of kidney function [8]. This indication aims at the secondary prevention of CKD, and the role of dietary protein and phosphorus restriction to slow progression of CKD has been the focus of this goal [8]. The other indication is to reduce the accumulation of potentially toxic compounds in CKD patients and also to prevent or treat protein−energy wasting (PEW) [9,10]. This indication can be viewed as the tertiary prevention of CKD progression. Detailed components of the dietary interventions for these two indications have much in common, but the patients that are addressed by these two interventions differ by the stages of their CKD. The relative interest by the medical community in these two potential roles for the treatment of CKD has varied greatly, at least since the 19th century [11].

Protein intake

The amount of protein intake affects CKD patients in three ways: the first is that protein intake per se increases the GFR of the failing kidneys; the second is the metabolites derived from the protein ingested may act as uremic toxins, some of which, such as indoxyl sulfate or hydrogen ion, may worsen kidney function; and the third is that foods or food ingredients that contain much protein may also contain excessive amounts of such other solutes phosphate and potassium. Therefore reduction of dietary protein intake has been used to ameliorate the progression of renal failure via such mechanisms as attenuation of hyperfiltration or reduced single nephron hypertrophy induced by the protein load to the failing kidneys or by the reduction in the accumulation of uremic and nephrotoxic substances. In addition, reduction in protein intake by reducing the accumulation of uremic toxins may postpone the time until RRT is required.

Metaanalyses indicate that protein restriction does delay the need for RRT [4,12]. Whether this effect is due, in part, to suppression of the rate of progression of renal disease and loss of GFR or is exclusively the result of a lower rate of generation of uremic toxins is unclear. Even in patients with far-advanced CKD who might commonly be placed on RRT, low-protein diets (LPDs) have been shown to delay the need for chronic dialysis therapy.

Brunori et al. demonstrated this in a randomized, prospective controlled trial that investigated the effectiveness of supplemented very low protein diets (SVLPD) with a mixture of ketoacid and hydroxyacid analogs of five essential amino acids and four other essential amino acids. Predialysis patients without diabetes mellitus who were older than 70 years and had a GFR of 5−7 mL/min were studied [13]. Patients were randomized to either begin maintenance dialysis ($n = 56$) or to receive SVLPD ($n = 56$), which provided 35 kcal/kg/day and 0.3 g/kg/day of protein supplemented with ketoacids or one hydroxyacid, essential amino acids, and vitamins. A total of 40 (71%) of the patients assigned to the SVLPDs started chronic dialysis after 6−20 months of dietary therapy; the patients delayed dialysis initiation by a median period of 10.7 months without evidence of worse outcomes as compared to the group that started dialysis at the onset. A total of 31 (55%) patients died in the dialysis group and 28 (50%) patients in the diet group during a median follow-up period of 26.5 months. Unadjusted survival was not different between the two groups, although after adjustment for the greater age and higher prevalence of cerebral vasculopathy in the SVLPD group, there was significantly greater survival in the diet group by per-protocol analysis but not by intention-to-treat analysis. The number of hospitalizations and days of hospitalization per patient-year were significantly less ($P < .001$ and $P = .02$) in the SVLPD group, although these differences disappeared if hospitalizations for the placement of the first dialysis access in the diet group were included in these calculations. These findings strongly suggest that dietary therapy can safely delay the need for chronic dialysis for several months in selected pre-ESRD (end-stage renal disease) patients. LPDs or SVLPDs may also provide advanced CKD patients with sufficient time for the placement and maturation of a permanent hemodialysis (HD) vascular access or peritoneal dialysis catheter without requiring the use of temporary catheters needed to inaugurate dialysis urgently.

Energy intake

The importance of adequate energy intake was shown in a study that investigated nitrogen balance and urea nitrogen appearance in advanced CKD patients who received different energy intakes [14]. A number of 6 nondialyzed patients with advanced CKD [the mean estimated GFR (eGFR) calculated from the mean of the creatinine and urea clearance was 7.8 ± 4.3 SD mL/min] were each assigned to ingest diets providing energy intakes of 25, 35, or 45 kcal/kg/day; the order of administration of these three energy intakes was determined in random fashion. In addition, two of the patients were assigned diets providing only 15 kcal/kg/day. Dietary protein intake for all patients was 0.55−0.60 g protein/kg/day with all four diets and was constant for each patient throughout the period of their study. Each of the dietary energy intakes was consumed for a mean of 23.7 ± 5.7 SD days. A total of 16 metabolic balance studies were performed on two, five, five, and four patients fed 15, 25, 35, and 45 kcal/kg/day, respectively. Changes in body weight during each study period were determined in two, five, five, and three patients fed an energy intake of 15, 25, 35, and 45 kcal/kg/day, respectively. The study demonstrated that three out of four individuals taking the energy intake of 25 kcal/kg/day showed negative nitrogen balance, while only one of five and four participants had negative nitrogen balance with the 35- and 45-kcal/kg/day energy intakes, respectively. Body weight decreased in two of five patients with 25 kcal/kg/day, while body weight increased in four of five and all three patients who were provided with 35 and 45 kcal/kg/day, respectively. These data indicate that patients with advanced CKD appear to require an energy intake of about 35 kcal/kg/day to maintain neutral or positive nitrogen balance and stable body weight [14]. An animal model of kidney disease demonstrated that a high-calorie diet can ameliorate disturbances of lipid metabolism in remnant kidneys [15].

A post hoc evaluation of the Modification of Diet in Renal Disease (MDRD) study found that the participants randomly assigned to the SVLPD diet experienced an increased risk of death over a 10-year period of follow-up [16]. A total of 49 patients assigned to the SVLPD died (38.9%, 21% due to cardiovascular causes), whereas only 30 patients assigned to the LPD died (23.3%, 16% due to cardiovascular deaths). The hazard ratio (HR) for death was 1.92 (95% CI, 1.15−3.20) in the fully adjusted model. It is not clear how the increased mortality in the SVLPD group could be related to their diet, particularly because the post hoc follow-up was to years and the mean duration of treatment time for the patient on the MDRD protocol was only 2.2 years. Moreover, it would have been very difficult for any patient in the MDRD study to obtain access to the ketoacids-essential amino acid mix once they left the MDRD study.

The MDRD study also indicated that it was not easy to maintain an adequate energy intake on the LPD and SVLPD diets. The patient's energy intake decreased from 25.0 ± 6.7 and 25.5 ± 6.5 kcal/kg body weight (BW)/day at the baseline in the LPD and the SVLPD groups, respectively, to 21.9 ± 4.6 and 22.0 ± 4.7 kcal/kg BW/day during the follow-up period in the LPD and the VLPD groups [16]. The energy intakes in the LPD and SVLPD patients in the MDRD study were lower than the lowest energy intake in the abovementioned nitrogen balance study, which was 25 kcal/kg/day and did not maintain the nitrogen balance or body weight in nondialyzed advanced CKD patients [14]. These findings suggest that it can be challenging to maintain adequate energy intake with the LPD or SVLPD diets; this reduced energy intake might lead to deterioration in clinical outcomes. Indeed, the patients who were assigned to the LPD or SVLPD diets in the MDRD study lost weight [17].

Many studies have reported that the energy intake of CKD patients in the real world is far less than is recommended. A study investigated 539 patients with stage 3+ CKD in Taiwan and demonstrated that their dietary energy intake was also less than that recommended by dietitians across all CKD stages [18]. Another study obtained similar results. This study, performed in Brazil, investigated the dietary protein and energy intake of 454 participants with reduced kidney functions (eGFR 38.4 ± 14.6 mL/min/1.73 m^2) [19]. The investigators found that the patients' median dietary energy intake was 25.0 kcal/kg/day (IQR, 19.5−33.0 kcal/kg/day) and median protein intake was 1.1 kcal/kg/day (IQR 0.9−1.4 kcal/kg/day).

Efforts have been made to meet the daily energy requirements of patients with CKD [20−22]. The baseline the dietary protein and energy intakes and nutritional markers in the MDRD study were investigated according to the patient's GFR levels [23]. The investigators found that the dietary energy intake was lower than the recommended values, especially in the patients with the lower GFR levels. The amount of dietary energy intake (mean ± SD) calculated from interviews by dietitians were 26.4 ± 6.90 ($P < .01$ vs GFR >37 group), 29.2 ± 10.0 ($P < .05$ vs GFR >37 group), and 31.0 ± 9.30 kcal/kg/day in men and 24.6 ± 8.58 ($P < 0.01$ vs GFR >37 group), 27.9 ± 8.58, and 27.7 ± 8.84 kcal/kg/day in women with GFR levels of <21, 21−37, and >37 mL/min/1.73 m^2, respectively.

A similar trend was observed with regard to the patients' dietary protein intakes. The patients with the lower GFR levels exhibited poorer nutritional measures as compared to those with the higher GFRs. These associations were attenuated after adjustment for the different dietary energy and protein intakes of the patients, which suggests that the poorer nutritional status found in the advanced CKD patients may be due to the decreased dietary intake. It is noteworthy that 657 individuals out of 1785 patients in the study population reported that their protein and/or energy intake was recommended to be reduced [23].

Another question is whether the type of dietary protein influences the ease of maintaining an adequate energy intake with LPDs. This was investigated in six nondialyzed CKD patients fed two LPDs [about 0.6 g protein/kg ideal body weight (IBW)] that contained either 70% animal protein or 30% animal protein [24]. Daily energy expenditure was estimated from the patient's measured resting energy expenditure and the patient's activity levels. The mean serum creatinine level of the six CKD patients was 300 μmol/L. The patients' diet was changed from a conventional LPD providing 70% animal protein to a 30% animal protein diet that was ingested for at least 2 weeks. Total protein intake was similar with both diets, 0.70 ± 0.05 g/kg IBW/day (mean ± SD) and 0.73 ± 0.11 g/kg IBW/day ($P = .638$), with the 70% and 30% animal protein diets, respectively. The dietary energy intake increased slightly, from 27.8 ± 6.1 (SD) kcal/kg IBW/day to 31.4 ± 7.0 kcal/kg IBW/day ($P = .094$), when the patients changed from the 70% animal protein diet to the 30% animal protein diet. However, four of six patients eating the 70% animal protein diet and three of six patients ingesting the 30% animal protein did not eat an amount of calories that equaled their calculated daily energy expenditure [24]. Since plant-derived foods are often a major source of dietary protein in CKD patients, protein-free foods may be added to ensure that energy intake is adequate.

Importance of monitoring the patient

Patients with advanced kidney disease are prone to experience malnutrition and wasting. The International Society of Renal Nutrition and Metabolism has publicized the concept of PEW [25]. PEW is manifested by abnormalities and/or reductions in serum chemistries, body mass, muscle mass, and dietary protein and energy intake. Tools have been described for assessing the presence and severity of PEW; these include appetite, food intake, energy expenditure, body mass and composition, laboratory markers, and nutritional scoring systems [25]. Patients with advanced CKD who are treated with dietary therapy should be repetitively monitored with these markers to assess whether they have developed signs of PEW.

Serum chemistries

Serum albumin is synthesized by the liver, and its production is affected by nutritional status [26,27], inflammation, and acidemia [28]. Serum albumin has a strong and consistent role in predicting mortality and morbidity, especially in chronic dialysis patients [25]. Several factors affect the serum albumin level in patients with advanced kidney disease in addition to nutritional, inflammatory, and acid–base status. Low serum albumin levels are associated with the severity of proteinuria in diabetic nephropathy and with the rate of progression of renal disease [29]. An extrapolation from the accumulated evidence in patients undergoing maintenance dialysis [30] suggests that volume expansion or overhydration may also lower the serum albumin level.

Transthyretin is another serum protein that can be associated with the nutritional or protein–energy status of the patient. Little evidence has been obtained regarding the serum transthyretin level as a nutritional marker in CKD patients not on dialysis, although several studies have investigated in dialysis patients [31,32]. A cross-sectional study investigated the association between serum transthyretin and nutritional or protein–energy status, as indicated by body mass index (BMI), in CKD patients with or without RRT [33]. The authors found that a significant positive association between serum transthyretin and BMI ($r = 0.20$, $P = .02$) in the entire cohort, while the C-reactive protein level was negatively associated with the serum transthyretin concentration [33]. The significance of maintaining healthy nutritional or protein–energy status in patients with advanced CKD was illustrated by an observational cohort study that investigated the association between the protein–energy status at the inception of dialysis treatments and patient survival thereafter [34]. This study included 167 incident chronic dialysis patients (HD, 57.5%) and assessed the baseline demographics and such protein–energy indices as BMI, serum albumin, and subjective global assessment (SGA) score. Both a low-serum albumin less than 3.3 g/dL and an SGA score of B and C indicating the presence of PEW were significantly associated with the higher risks of all-cause mortality (HR 1.86, 95% CI 1.17–2.97, $P = .01$ and HR 1.74, 95% CI 1.11–2.72, $P = .02$, respectively) during a median follow-up of 53.0 months (IQR, 23–83 months) [34].

Body weight

The trajectory of body weight change before initiation of dialysis therapy can be associated with worse outcomes after starting dialysis treatment. A study investigating a total of 3933 patients in the CRIC study and 1067 participants in the AASK study assessed the association between the GFR level and body weight change and between body weight change prior to dialysis and all-cause mortality after the commencement of chronic dialysis. [35]. A similar trend of body weight change was found in both the CRIC and the AASK studies, whereby there was a substantial decline in body weight after the eGFR, estimated from cystatin C and the CKD-EPI equation, decreased to about 35 mL/min/1.73 m^2. In the CRIC study, every 10 mL/min/1.73 m^2 further decline in eGFRcys was associated with a mean decrease of 1.45 (95% CI, 1.19–1.70) kg in body weight, and a mean decline of 0.31 (95% CI 0.21–0.40) kg/m^2 in BMI. In the AASK study patients, there was a mean decrease in body weight of 2.3 (95% CI, 2.1–2.4) kg, and a mean reduction in BMI of 0.79 (95% CI 0.73–0.86) kg/m^2 for every 10 mL/min/1.73 m^2 decline. During a median follow-up period of 3.3 years (IQR, 1.5–4.8) in 770 participants in the CRIC study, the annual percent weight change between the time when eGFR reached 35 mL/min/1.73 m^2 and the time of initiation of dialysis therapy was significantly associated with the survival rate of the patients. The adjusted HR for mortality for participants who had larger annual declines in body weight of 5% or more per year was 1.54 (95% CI 1.17–2.03) as compared to participants whose annual changes in body weight were between −5% and +5% per year. A similar association between change in body weight and survival was observed in the AASK study (HR 1.56, 95% CI, 1.06–2.30) [35].

Another study including a total of 11,090 nursing home residents examined the association between the body weight changes during the 3–6-month period before the initiation of chronic dialysis and 1-year survival after starting dialysis [36]. This study demonstrated that the median decrease in body weight during this period was −6% (IQR −13%, +1%). Percent body weight change was categorized into quintiles, namely, −59% to 15%, −14% to −9%, −8% to −4%, −3% to 3%, and 4% to 58%. Participants in the first, second, and fifth quintiles of the changes in body weight experienced worse survival as compared to the reference group of the fourth quintile; mortality HRs in the first, second and fifth quintiles of weight change were 1.35 (95% CI 1.25, 1.47), 1.07 (95% CI 1.00, 1.17), and 1.24 (95% CI 1.14, 1.35), respectively [36].

Composite scores

Several composite scores of protein–energy status and inflammation, including SGA, MIS (malnutrition–inflammation score, also known as the Kalantar score), and MNA (mini nutritional assessment) have been developed to assess the protein–energy status of the patients. These scores have been extensively investigated with regard to their association with clinical outcomes in the dialysis population [37–40]. However, only a limited number of studies have investigated the validity of these composite scores in nondialyzed advanced CKD patients.

A cohort study investigated the association between the protein–energy status, assessed by the four-point SGA scale, and all-cause mortality during a 5-year follow-up period [41]. A total of 1031 CKD patients (732 nondialysis CKD stage 1–5 patients and 299 chronic dialysis patients) were included in this study. PEW assessed by SGA (PEW_{SGA}) was defined as an SGA score of more than 1. A PEW_{SGA} was associated with a significantly higher risk of death, with an RR of 1.19 (95% CI, 1.08–1.31, $P = .0003$) and 1.15 (95% CI 1.07–1.23, $P < .0001$) in the nondialyzed and chronic dialysis patients, respectively [41].

Another study investigated the association between the MIS and survival of 300 nondialyzed CKD stage 3–5 patients [42]. A high MIS was significantly associated with an increased prevalence of advanced CKD in these patients ($P < .001$). MIS was also significantly associated with higher risks of death during a median follow-up of 30 (IQR, 18–37) months. The HR for death in 300 patients was 1.09 (95% CI 1.02–1.17) per unit increase in the MIS. Patients in the group with the highest tertile of MIS exhibited a higher risk of death (HR 2.59, 95% CI, 1.31–5.11) compared to the lowest tertile group. The group with MIS > 3 had a HR for death of 1.93 (95% CI 1.07–3.49) compared to the group with MIS ≤ 3 [42].

Benefit beyond dialysis initiation

Inadequate nutritional intake in patients with advanced CKD is of substantial concern, because PEW is common in patients who are beginning dialysis therapy [43]. In the authors' experience, patients often describe weight loss during the 3–6 months preceding their commencement of chronic dialysis therapy, a finding similar to that reported in nursing home patients starting dialysis [36]. Tortorici et al. observed that a decrease in serum albumin during the months before patients with advanced CKD began chronic dialysis.

These findings are troubling because patients starting chronic dialysis who have PEW have increased mortality [43]. As a result, patients who started dialysis therapy experience worse survival during the first several months (Fig. 30.1). However, substantial data indicate that LPDs and SVLPDs, when properly prescribed, do not engender PEW [10,44]. These findings raise the possibility that properly prescribed dietary therapy in patients approaching ESRD might reduce their mortality risk after they commence chronic dialysis treatment, a thesis that would seem well worth testing [45,46].

The foregoing considerations suggest that LPDs or ketoacid or essential amino acid–SVLPDs may be able to safely delay the need for chronic dialysis therapy by reducing the generation of uremic toxins, independent

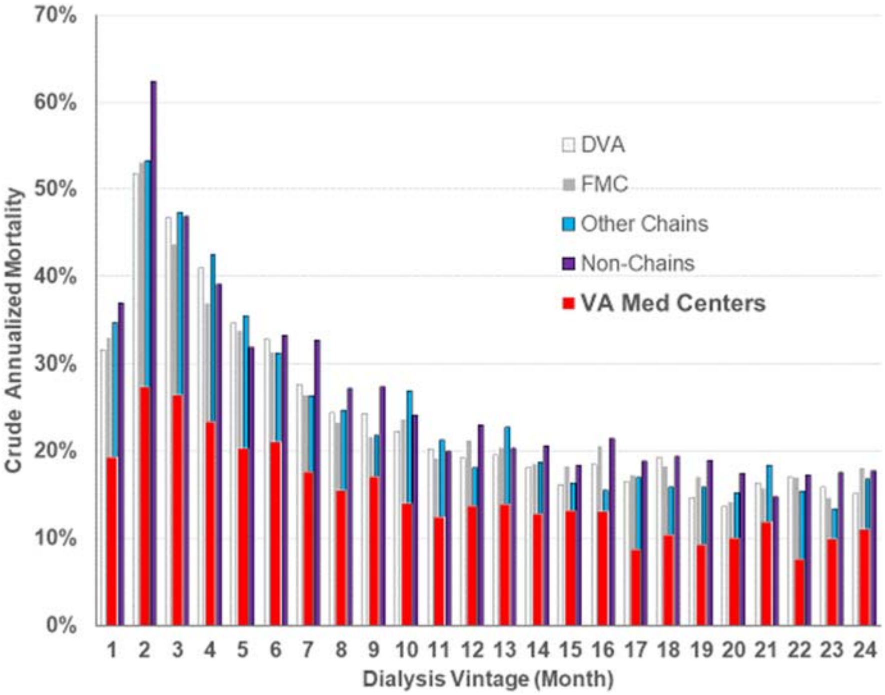

FIGURE 30.1 High mortality rate during the first 12 months of hemodialysis therapy in more than 52,000 incident ESRD veterans in the United States over 4 years (10/2007–9/2011). *DVA*, DaVita Kidney Care; *ESRD*, end-stage renal disease; *FMC*, Fresenius Medical Care; *VA Med Centers*, Veterans Affairs Medical Centers. *Source: Adapted from the Transition of Care in Chronic Kidney Disease Chapter of the United States Renal Data System Annual Data Report.*

of whether the rate of decline of GFR is diminished. The clinical trial of Brunori et al. [13] is pertinent in this regard. These investigators showed that selected stage 5 CKD patients with a GFR of 5–7 mL/min who were prescribed SVLPDS could safely delay their need for chronic dialysis therapy.

LPDs (i.e., 0.6 g protein/kg/day) and SVLPDs may also provide patients with advanced CKD with sufficient time for placement and maturation of a permanent HD vascular access or peritoneal dialysis catheter without requiring the use of temporary catheters needed to inaugurate dialysis urgently [47]. Mortality increases when people commence chronic dialysis [48]. Functionality decreases in nursing home residents when they begin dialysis [49]. If these adverse events are related to dialysis treatment per se, this may provide another indication for the use of LPDs and SVLPDs to delay the initiation of dialysis. More randomized, prospective clinical trials (RCTs) are needed to define the roles of dietary therapy for people with far-advanced CKD.

Dietary therapy for incremental or infrequent dialysis

LPD and SVLPD therapy has another role for patients with advanced CKD who selected incremental or infrequent dialysis (Table 30.1). These dialysis regimens are performed in the schedule with once or twice weekly compared with the ordinary thrice-weekly HD treatment [50]. Patients whose kidney function has declined to the degree to which chronic dialysis is required but is sufficiently high that standard thrice-weekly HD or daily peritoneal dialysis may not be necessary to minimize uremia may benefit from these regimens [51]. To control uremic toxicity, an attenuated dose of dialysis may be offered to these patients, which will be augmented by the residual renal function (RRF), for example, once- or twice-weekly HD or a similarly reduced dose of chronic peritoneal dialysis (Table 30.2). As RRF, that is, the GFR of the native kidneys continues to decrease while these patients receive incremental dialysis, uremic toxins may accumulate, and the dose of chronic dialysis is progressively increased until the patient is receiving standard doses of chronic dialysis therapy. In practice, many nephrologists simply use infrequent dialysis, wherein the patient receives a rather fixed dose of infrequent dialysis until RRF declines to a degree that signs of uremia begin to become prominent and standard dialysis therapy is instituted (Fig. 30.1).

Clinical trials and epidemiologic studies suggest that this treatment may offer several advantages to the patient. Patients, especially older patients, may find the treatment regimen preferable to a more demanding standard full-dose regimen of chronic dialysis therapy. Incremental or infrequent dialysis may provide patients with the time needed to rearrange their lifestyle appropriately or become more emotionally adjusted to chronic dialysis therapy [52]. Lower or less frequent doses of dialysis seem to delay the decline in

TABLE 30.1 Nutritional management of incremental hemodialysis (HD): strategies for dialysis commencing from once-weekly to higher frequencies.

	Once-a-week	Twice-a-week	Thrice-a-week
Nutritional support	+++	++	+
Protein intake	Reduced (e.g., 6 out of 7 days): SVLPD	Reduced (e.g., 5 days): SVLPD or LPD	Increased
Energy intake	Increased	Increased	Increased
Vascular access compromise	+	++	+++
Protection of residual renal function	+++	++	−/+
"Counter-physiologic" effect of HD treatment	+	++	+++
HD scheduling challenge	+	++	−
Costs and reimbursement	+	++	+++

LPD, Low-protein diet; *SVLPD*, supplemented very low protein diet.

TABLE 30.2 Proposed decision support system with 11 criteria for initiating and maintaining incremental (twice-weekly) hemodialysis (HD) treatment upon transition to end-stage renal disease, and for incremental transition to thrice-weekly HD.

Incremental (twice-weekly) HD treatment criteria

1. Adequate residual kidney function with a urine output >600 mL/day (transition to thrice weekly if urine output drops to <500 mL/day)[a]
2. Limited fluid retention between two consecutive HD treatments with a fluid gain <2.5 kg (or less than 5% of the ideal dry weight) without HD for 3–4 days
3. Limited or readily manageable cardiovascular or pulmonary symptoms without clinically significant fluid overload[b]
4. Suitable body size relative to residual renal function; patients with larger body size may be suitable for twice-weekly HD if not hypercatabolic
5. Hyperkalemia ($K > 5.5$ mEq/L) infrequent or readily manageable
6. Hyperphosphatemia ($P > 5.5$ mg/dL) infrequent or readily manageable
7. Good nutritional status without a florid hypercatabolic state
8. Lack of profound anemia (hemoglobin > 8 g/dL) and appropriate responsiveness to anemia therapy
9. Infrequent hospitalization and easily manageable comorbid conditions
10. Satisfactory health-related quality of life and functional status
11. KRU > 3 mL/min/1.73 m^2 (transition to thrice-weekly if KRU < 2 mL/min/1.73 m^2)

Implementation strategies

1. To initiate twice-weekly HD, the patient should meet the first (urine output >600 mL/day) and the last criteria (KRU > 3 mL/min/1.73 m^2), plus most (five out of nine) other criteria
2. Examine these criteria every 1–3 months in all twice-weekly HD patients and compare outcome measures between twice- and thrice-weekly HD patients to assure outcome noninferiority for continuation of twice-weekly HD
3. Consider transition from a twice-weekly to thrice-weekly HD regimen if patient's urine output drops <500 mL/day, if KRU declines <2 mL/min/1.73 m^2, or if patient's nutritional status or general health condition shows a deteriorating trend over time

[a] *The minimum required urine output to initiate twice-weekly has been changed to 600 mL/day in this adaptation, while >500 mL/day is needed to maintain twice-weekly regimen.*

[b] *Lack of systolic dysfunction (EF > 40%) and no major coronary intervention over the past 3 months.*

KRU, Residual urea clearance.

Adapted from Kalantar-Zadeh et al. Am J Kidney Dis 2014;64(2):181–186.

residual GFR, improve quality of life, possibly decrease mortality rates, and reduce health care costs [50–54]. In fact, higher levels of RRF are associated with reduced mortality rates in both patients undergoing chronic peritoneal dialysis and patients receiving chronic HD [55,56]. One epidemiologic study indicated that compared with patients treated with standard thrice-weekly HD, patients with renal urea

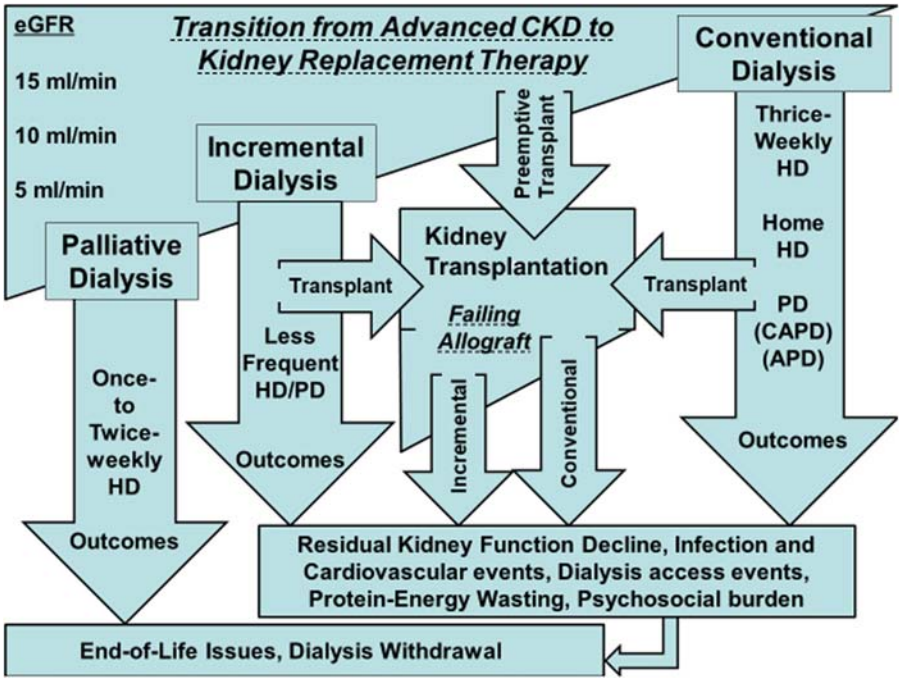
eGFR
15 ml/min
10 ml/min
5 ml/min
Transition from Advanced CKD to Kidney Replacement Therapy
Conventional Dialysis
Incremental Dialysis
Palliative Dialysis
Preemptive Transplant
Kidney Transplantation
Failing Allograft
Transplant
Transplant
Thrice-Weekly HD
Home HD
PD (CAPD) (APD)
Less Frequent HD/PD
Once- to Twice-weekly HD
Incremental
Conventional
Outcomes
Outcomes
Outcomes
Residual Kidney Function Decline, Infection and Cardiovascular events, Dialysis access events, Protein-Energy Wasting, Psychosocial burden
End-of-Life Issues, Dialysis Withdrawal

FIGURE 30.2 Transition from advanced chronic kidney disease (eGFR < 30 mL/min/1.73 m^2) to renal replacement therapy with different modalities, also highlighting intermodality transitions and impact on clinical outcomes.

clearances >3.0 mL/min/1.73 m^2 may survive longer on once-weekly dialysis with a slower loss of RRF; but those with renal urea clearances ≤3.0 mL/min/1.73 m^2 may have greater mortality [50]. These findings indicate that the RRF and incremental dialysis are mutually interdependent. Incremental dialysis may preserve RRF, and RRF itself is indispensable for the clinical benefits of incremental dialysis.

Two metaanalyses were performed that compared incremental dialysis, including HD or peritoneal dialysis, with conventional full-dose dialysis. One metaanalysis, including 11 observational cohort studies, was performed on patients receiving incremental HD or peritoneal dialysis in comparison with the standard, full-dose dialysis [57]. This study investigated the associations between these dialysis modalities and all-cause mortality, RRF loss, and time to full-dose dialysis. Incremental dialysis was not significantly associated with any higher risk of all-cause mortality (HR, 1.14, 95% CI 0.85, 1.52). Moreover, the loss of RRF was smaller or RRF was more preserved with incremental dialysis as compared with patients on full-dose dialysis; the decline in RRF was −0.13 (95% CI, −0.18, −0.08) and −0.74 (95% CI, −1.15, −0.33) mL/min/month in incremental dialysis and full-dose dialysis, respectively. The mean difference between the two groups was 0.58 (95% CI, 0.16, 1.10) mL/min/month in the random-effects model ($P = .007$). The overall mean time to full-dose dialysis was 12.1 months (95% CI 9.8, 14.3) with a random effects model [57] (Fig. 30.2).

The other metaanalysis investigated the effects of incremental HD, as compared to standard HD, on mortality, renal function, urinary volume, and laboratory measures [58]. The study included 15 observational studies and one cross-sectional study. The group receiving incremental HD had greater survival (RR, 0.80, 95% CI 0.73, 0.87, $P < .001$, $I^2 = 0\%$), better preservation of renal function (standardized mean difference: 0.68, 95% CI 0.04, 1.32, $P = .039$, $I^2 = 92.7\%$), and urinary volume (weighted mean difference: 333.4, 95% CI 86.8, 579.9, $P = .008$, $I^2 = 92.7\%$). The low I^2 values indicate that in these studies the heterogeneities were low with regard to survival but were considerably higher with regard to the preservation of renal function and urinary volume. The metaanalysis also compared serum calcium, phosphorus, albumin, and blood hemoglobin at the end of the follow-up period or the changes in these measures between the beginning and the end of follow-up in the patients receiving incremental HD versus full-dose HD. The laboratory measurements did not differ between the two groups, except for the serum calcium levels and blood hemoglobin levels at the end of the follow-up period, which were lower to a small but statistically significant degree in the incremental HD group. Hospitalization also did not differ between the groups [58]. Patients receiving incremental dialysis seemed to have their uremic symptoms mitigated as much as patients receiving standard dialysis therapy [51]. Unfortunately, the protein intake was not investigated or compared in these metaanalyses, although Garofalo et al. described a renal replacement regimen consisting of once-weekly HD combined with a dietary intervention consisting of a low protein, low phosphorus, and high-energy diet. They also discussed the importance of utilizing dietary and pharmacological therapy to augment the effectiveness of incremental RRT [57].

Because well-designed LPDs and SVLPDs will reduce the load of many potentially toxic solutes that accumulate in kidney failure, the combination of incremental dialysis and dietary therapy may provide ESRD patients who have substantial RRF with the benefit to safely delay standard dialysis therapy. Indeed, some investigators have combined once- or twice-weekly dialysis with well-defined dietary management LPDs or SVLPDs [52,53,59,60].

Locatelli et al. investigated the effects of the integrated diet dialysis program on its feasibility, its effect on nutritional status, and the removal of solutes and water [52]. The program consisted of a dietary intervention with an LPD (0.4 g/kg IBW/day) supplemented with essential amino acids or a mixture of essential amino acids and ketoacid analogs combined with once-weekly HD. The goal was to maintain the predialysis serum urea level below 90 mg/dL (i.e., a predialysis serum urea nitrogen, SUN or BUN, level below 42 mg/dL). The mean baseline GFR was 2.54 ± 0.94 mL/min. The patient and technical survival rates were 89% and 56%, respectively, at the end of the 12-month follow-up period. Protein–energy factors, including body weight, lean body mass, fat mass, plasma proteins, albumin, transferrin, and C3 and C4 complement components, remained stable throughout the follow-up period, although the creatinine appearance rate and nerve conduction velocities were decreased at the end of the follow-up period [52].

In another more recent multicenter, nonrandomized, prospective controlled study of 68 incident CKD patients with a GFR between 5 and 10 mL/min/1.73 m^2 who were followed in predialysis clinics, a combination of infrequent HD and an LPD (a Combined Diet Dialysis Program, CDDP) was compared to a standard thrice-weekly HD schedule and free-choice diet (the THD group) [53]. The CDDP consisted of a weekly HD schedule and an LPD (0.6 g/kg/day) with adequate energy (30–35 kcal/kg/day) and low phosphorus (600–700 g/day), and low sodium that was fed on the nondialysis days. Patients in the CDDP group ($n = 38$), as compared to the THD patients ($n = 30$), maintained greater urinary output and RRF after 12 months and had a lower erythropoietin resistance index, a lower β2 microglobulin level, stable protein–energy status, and a lower need for cinacalcet and phosphate binders. The survival rate in the CDDP patients was similar to the THD group, whereas the hospitalization rate was lower in the CDDP patients than in the THD group during a follow-up period of 24 months [53].

The result of this study indicates that some but not all patients treated with diet and incremental dialysis are able to safely delay their need for standard dialysis treatment. Although HD may cause catabolic, inflammatory, and hemodynamic stresses, LPDs and SVLPDs seem to maintain good protein–energy and metabolic and clinical status and result in a slower loss of RRF [53,59,60], possibly because HD is performed less frequently. The required dose of ESA may decrease because infrequent HD lessens the loss of blood [53]. Blood loss due to HD treatment can be substantial. Strongly motivated patients who are more knowledgeable about CKD seem to adjust better to this diet and infrequent dialysis regimen [52,53].

LPDs or SVLPDs are not uncommonly prescribed with these dialysis regimens. However, the extent to which the apparent benefits of incremental or infrequent dialysis are due to or require treatment with these diets is not known. Indeed, there are no RCTs that compare outcomes with either incremental or infrequent dialysis with those of standard thrice-weekly HD or that compare incremental dialysis with LPDs or SVLPDs with incremental dialysis without such diets. RCTs are needed to confirm whether incremental or infrequent dialysis does induce these benefits and the degree to which LPDs or SVLPDs contribute to the apparent benefits of less frequent dialysis. In some studies of incremental dialysis, the frequency or dose of dialysis was not increased as the GFR continued to fall. This latter type of treatment should probably be considered to be infrequent dialysis rather than incremental dialysis.

Future directions

The CKD patients who are more likely to benefit from LPDs and SVLPDs, and the level of reduced GFR at which these diets should be implemented, need to be better defined. Randomized controlled clinical trials should help in this regard. One approach would be to prescribe these diets with incremental dialysis when it is considered time to start maintenance dialysis therapy. Such dietary therapy could be integrated into a more general plan for the nutritional management of CKD patients since the authors believe that a strong case can be made to start some form of dietary therapy at substantially higher GFRs. This is particularly the case for controlling sodium, potassium, phosphorus, and calcium balance and maintaining adequate energy intake so as to prevent PEW. Protein restriction at higher levels of GFR may also ameliorate more subtle uremic symptoms. Current data suggest that patients need a minimum GFR level—possibly a urea clearance ≥ 2–3 mL/min/1.73 m^2—to do well with dietary therapy [46]. Patients being considered for dietary therapy probably should not suffer from severe acute or chronic catabolic illness, should be able to understand the purpose and potential benefits of dietary therapy, should have self-discipline, and should be strongly motivated. This review does not address the question of whether dietary therapy can retard the progression of kidney failure.

We need a clearer understanding of the extent to which dietary therapy will maintain both pre-ESRD and ESRD patients in good nutritional and metabolic status, safely prevent and ameliorate various manifestations of uremia, and, thereby, delay the need for RRT independent of any effect on the rate of decline of GFR. The optimal intake of protein, amino acids, and other needed nutrients for these patients needs more careful definition. The role of LPDs and SVLPDs for patients receiving incremental or infrequent dialysis requires more investigation, particularly with regard to defining patients who are good candidates for such treatment, optimal dietary therapies for this regimen, and techniques for increasing dialysis treatment as RRF declines. Whether intestinal sorbents or binders (e.g., activated charcoal to bind indoxyl sulfate) can safely and effectively augment dietary management also needs investigation [61].

Another challenge is improving the patient's adherence to dietary therapy. Aparicio et al. [20] observed that about 50% of patients with CKD adhere satisfactorily to SVLPDs. This may be an overly optimistic estimate for the general CKD population, perhaps due to the types of patients referred to Aparicio et al. [20] and their clinical expertise. However, for pre-ESRD and ESRD patients, the prospect of commencing chronic dialysis therapy or undergoing more frequent (i.e., standard dose) dialysis often engenders much anxiety, which may increase the patients' motivation for dietary adherence. Clearly, not every patient with CKD will adhere to LPDs or SVLPDs.

Finally, it would be of value to improve the training of nephrologists concerning the nutritional management of CKD and to provide the convincing evidence to nephrologists that some dietary therapies can benefit patients with CKD. The ease with which nephrologists can provide nutritional therapy might be facilitated. The National Health and Nutrition Examination Survey data indicate that American men and women with stage 4 or 5 CKD have mean protein intakes of 1.03 and 0.99 g protein/kg IBW/day, respectively, which is substantially greater than currently recommended intakes [62]. This probably reflects, in part, the reluctance of nephrologists to prescribe protein restriction. One solution for this reticence might be to develop centers of excellence for nutritional therapy staffed by renal dietitians. Physicians could easily and with minimal effort refer patients with stage 4 or 5 CKD to these centers. Such centers could be economically feasible, at least in urban areas with larger population densities. Clearly, more research is required to examine these possibilities and clarify the potential uses of nutritional therapy for patients with far-advanced CKD.

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CHAPTER

31

Nutritional management of maintenance hemodialysis patients

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Introduction

Causes of protein-energy wasting in maintenance hemodialysis patients

Factors altering nutrient intake

The ability of a patient to consume a sufficient diet is often impaired in maintenance hemodialysis (MHD) patients due to reduced appetite [1–3]. This problem is fairly common in MHD patients. As many as 30%–50% of end-stage renal disease (ESRD) and MHD patients are reported to have anorexia. Protein and energy intakes are reduced. A number of studies show that measures that estimate protein and energy stores, muscle mass, fat mass, and serum cholesterol and albumin levels are robust predictors of survival in MHD patients. Remarkably, the energy intake in MHD patients is commonly reduced even more than what has been observed in sedentary individuals. A cross-sectional study in 331 MHD patients showed that 38% of these patients reported reduced appetite [3]. The reports of reduced appetite were associated with a statistically significant decrease in the protein equivalent of total protein nitrogen appearance (PNA) also referred to as protein catabolic rate (PCR). This study also showed that a reduced appetite is associated with markers of poor nutrition, such as reduced adequate protein and energy intake. Inadequate nutrient intake in MHD patients, therefore, is the single most serum levels of prealbumin (transthyretin), total cholesterol, and total iron-binding capacity (TIBC). Inflammatory markers such as serum interleukin-6 (IL-6), C-reactive protein (CRP), and tumor necrosis factor alpha (TNF-α) were increased. The MHD patients in this study with reduced appetite required higher doses of erythropoietin, reported lower quality of life, as measured by the SF-36 scoring system, and had increased mortality [3].

There are a multitude of reasons why MHD patients are susceptible to protein-energy malnutrition or the more general syndrome, protein-energy wasting (PEW). The diet of MHD patients is often very restrictive. Because MHD patients are at increased risk for salt and water gain, and hyperkalemia and hyperphosphatemia; these patients are generally prescribed low sodium, potassium, and phosphorus intakes which make their diets more restrictive and less palatable. The frequent presence of diabetes mellitus (DM) among MHD patients (55% in some studies) often makes the prescribed diet even more restricted. The difficulties for these patients to procure and prepare the foods for the prescribed diet because of physical, mental, or financial limitations and the effort involved in procuring and preparing these foods often make it difficult for the MHD patient to ingest the appropriate diet and, hence, to maintain an important factor in the development and maintenance of PEW.

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Loss of nutrients during hemodialysis

Loss of amino acids during hemodialysis (HD) has been examined by several investigators and is estimated to be approximately between 4 and 8 g during an HD session [4–6]. In fasting patients, Kopple et al. reported free amino acid losses of 4.5–7.7 g per HD session using a Kiil dialyzer with a glucose-free dialysate for 11 hours. Additionally, an average of 3.7 g (2.4–5.2 g) of bound amino acids (e.g., peptides) were lost into the dialysate. The loss of free amino acids increased to about 5–8 g per HD if these patients were fed during HD. When patients were dialyzed with dialysate containing a glucose concentration of 450 mg/dL (405 mg/dL of anhydrous glucose), there was a reduction in the free amino acid losses. With this glucose in the dialysate, free amino acid losses were 3.3 g in the fasted state and 6.0 g in the nonfasted states. Gutierrez et al. were not able to confirm that the addition of glucose to dialysate reduced amino acid losses [7]. However, Gutierrez et al. used a fairly standard dialysate glucose concentration of 180 mg/dL. Baxter cellulose acetate and Gambro GFS plus 20 hemodialyzers were used. Amino acid losses were 8.3 ± 0.9 SEM g and 7.9 ± 0.4 g with glucose and glucose-free dialysate, respectively. The difference may be due to the fact that the dialysate glucose, probably glucose monohydrate, concentration was only 180 mg/dL which would result in almost no uptake of dialysate glucose into the patient, whereas in the study of Kopple et al. with a dialysate glucose of 450 mg/dL, a substantial amount of glucose uptake by the patients would be anticipated.

Wolfson et al. reported free amino acid losses of 8.2 ± SD 3.1 g of free amino acids during a 5-hour HD session with a 1.5-m^2 hollow fiber dialyzer or 1.0- or 1.5-m^2 parallel plate dialyzers [5]. Amino acid losses increased, but only minimally, to 12.6 ± 3.6 g when patients were administered intravenous infusions of 39.5 g of amino acids and 200 g of d-glucose monohydrate during the HD. Hence, contrary to some concerns, the great proportion of infused amino acids is retained during an HD treatment.

Ikizler et al. used three different types of dialyzer membranes and examined amino acid losses during HD in MHD patients [6]. About 1 hour prior to HD, a small meal was taken. Patients undergoing MHD with high-flux polysulfone membranes lost 8.0 ± 2.8 g of amino acids per dialysis session. Patients who underwent HD using low-flux polymethylacrylate membranes lost 6.1 ± 1.5 g of amino acids. Those dialyzed with cellulose acetate membranes lost 7.1 ± 2.6 g of amino acids. These small differences in amino acid losses are biologically insignificant and are likely due to variations in blood flow rates and dialyzer surface area.

Protein losses during HD are very small. However, HD with high-flux polysulfone dialyzers (HFPS) with multiple reuses after bleach and formaldehyde treatments resulted in marked loss of proteins. Ikizler reported that after the sixth reuse of the HFPS, albumin losses became apparent [6]. While the albumin loss with the 15th use was 1.5 ± 1.3 SD per HD, by the 20th use it increased to 9.3 ± 5.5 g. A study by Kaplan et al. reported similar results [8]. Since these reports, polysulfone membranes have been manufactured differently to make them much more resistant to bleach.

Other factors that contribute to protein losses are leaking or clotted dialyzers, loss of blood that occurs with blood sequestration in the dialyzer (5–10 mL usually), blood loss from needle puncture sites and lab draws. These factors could account for 0.6–1.6 g of lost protein during a dialysis session [9].

Metabolic acidemia must be corrected as it has been shown to increase bone resorption and promote protein catabolism. Metabolic acidosis is highly prevalent (e.g., low serum bicarbonate before dialysis) in MHD patients [10–13]. The National Kidney Foundation Kidney Disease Outcomes Quality Initiative (KDOQI) Clinical Practice Guidelines recommend that serum bicarbonate concentrations should be maintained at 24–26 mEq/L [14]. Since some data suggest that even mild acidemia or low-normal arterial blood pH may be associated with negative nitrogen balance, we recommend maintaining the arterial blood pH at about 7.38–7.40 or the serum bicarbonate at around 24–25 mEq/L [15].

HD itself can be catabolic. Gutierrez et al. sham dialyzed ESRD patients with Cuprophan dialyzers (no dialysate used)and showed enhanced release of amino acids [16,17]. This amino acid release was not observed if these individuals were pretreated with prostaglandins, which suggests that prostaglandins may be involved in the genesis of dialysis-induced catabolism. Borah et al. reported data suggesting that HD induces catabolic state [18]. It is important to note that the nitrogen balance studies of Borah et al. were short term, and sufficient time was not allowed for equilibration after changing the dietary protein intakes.

Dialyzer membranes that are not adequately biocompatible can induce the release of proinflammatory cytokines (e.g., TNF-α, IL-1, IL-6, and others) by the activation of complement and leukocytes [19–21]. These proinflammatory cytokines can induce protein catabolism [22–24]. Oxidative stress may also play a role in the activation of the inflammatory cascade in MHD patients. Robust evidence indicates that inflammation is a cause of a hypercatabolic state in MHD patients [25]. Inflammation has been reported to play a central role in the malnutrition–inflammation–atherosclerosis syndrome [26]. Others have suggested that anorexia, inadequate nutritional intake, nutrient losses, and inflammation cause the PEW syndrome. PEW itself may promote inflammation, although clear evidence of this is lacking. The malnutrition–inflammation complex syndrome is one of the causes of PEW. Other causes of PEW include reduced nutrient intake, nutrient losses into hemodialysate [and occasionally into urine in MHD patients with substantial residual renal function (RRF)], increased circulating levels of some catabolic hormones (e.g., parathyroid hormone, glucagon) and resistance to anabolic hormones [e.g., insulin, growth hormone (GH), insulin-like growth factor-I (IGF-I)], acidemia, and carbonyl stress (see Chapter 13: Causes and Treatment of Protein-Energy Wasting in Kidney Disease) [27–29].

Other macro- and micronutrients may be lost during HD in addition to the removal of protein and amino acids. Gutierrez et al. found that during HD with glucose-free dialysate, about 26 g of glucose were removed [7]. When dialysate containing glucose (glucose monohydrate, 180 mg/dL) was used, about 30 g of glucose was absorbed. Similar results were reported by Wathen et al. [30]. Losses of water-soluble vitamins during HD are not large because the plasma concentrations of the vitamins are not high, the molecular weights of vitamins often are not small, and, in the case of vitamin B12, it is protein bound. Losses into dialysate may still be substantial for vitamins B1 (thiamin), B2 (riboflavin), B6 (pyridoxine), ascorbic acid, and folic acid [31–33]. Vitamin losses by MHD should easily be replaced by food intake and supplements as long as patients are eating well. Loss of vitamins via urine is negligible in MHD patients.

The importance of diet and PEW as patients approach and commence maintenance hemodialysis

At the time of initiation of MHD, the protein-energy status of the patient is a predictor of the patient's protein-energy status 1 or 2 years later [34–36]. Therefore it is important to monitor and prevent malnutrition from occurring before the inauguration of MHD. Protein-energy status may undergo improvement with the initiation of dialysis, but this similarity of the protein-energy status at the initiation of MHD to protein-energy nutrition status 1 or 2 years later remains true. Particularly in the predialysis stage [chronic kidney disease (CKD)-5], patients can become frankly anorectic and undergo deterioration in their clinical and nutrition status. It is, therefore, important to ensure a smooth transition to MHD from CKD stage 4 or 5. The NKF KDOQI guidelines recommend the initiation of chronic dialysis in individuals with advanced CKD if their nutritional status is not optimal and is due to uremia [14]. Patients with chronic renal failure (e.g., glomerular filtration rate <15–20 mL/min) who are not responding to vigorous attempts to optimize their protein and energy intakes and for whom there is no apparent cause for PEW other than low nutrient intake, the initiation of maintenance dialysis or treatment with a renal transplant is recommended.

Assessment of nutritional status in maintenance hemodialysis patients

Markers of nutritional and protein-energy status predict outcomes in dialysis patients, and, therefore, an assessment of nutritional and protein-energy status should be done at the initiation of dialysis as well as at monthly intervals (see Table 31.1). Predialysis serum albumin and creatinine, and body mass index (BMI) are independently associated with survival [37]. Data from the US Renal Data System (USRDS) and from large dialysis organizations concerning serum albumin and BMI confirm these findings [38]. In the Canada–USA (CANUSA) study, serum albumin and subjective global assessment (SGA) were independent predictors of death [39].

KDOQI guidelines recommend an assessment of nutritional status in MHD patients with a combination of measures rather than a single measure (see Table 31.1) [14]. Different aspects of protein-energy status are captured by utilizing measures of energy and protein intake, visceral protein pools, muscle mass, and dimensions of body composition. The effect of using the adjusted body weight [i.e., the patient's actual body weight adjusted for the standard body weight as determined by National Health and Nutrition Examination Survey (NHANES) 3] on clinical outcomes is not well defined [40]. Table 31.1 shows a list of parameters and tools to evaluate nutritional status and the time intervals for assessment as recommended by the KDOQI guidelines [14].

There are three categories in the KDOQI nutritional assessment guidelines. The first category includes measurements that should be routinely performed in all MHD patients. Examples are serum albumin and postdialysis body weight which should be measured monthly. Body weight as a percentage of standard body weight can be measured every 4 months. Because body weight and lean body mass may change and decline in MHD patients, it is important to compare these measurements to previous values [41,42]. There are no specific recommendations regarding BMI, but due to the ease of calculation it should be measured on a monthly to quarterly basis. Although BMI is a better measurement of body mass than body weight alone, both of these measures may be difficult to interpret because MHD patients frequently do not attain normal body water and sodium content postdialysis. Trends in body weight combined with simultaneous

TABLE 31.1 Recommended measures for monitoring nutritional status of maintenance hemodialysis patients adapted from Kidney Foundation Kidney Disease Outcomes Quality Initiative guidelines [14].

Category	Measure	Minimum frequency of measurement
I. Measurements that should be performed routinely in all patients	• Predialysis or stabilized serum albumin	• Monthly
	• % of usual postdialysis body weight, BMI*, and interdialytic weight gain*	• Monthly
	• % of standard (NHANES II) body weight	• Every 4 months
	• SGA	• Every 6 months
	• Dietary interview and/or diary	• Every 6 months
	• nPNA (nPCR)	• Monthly
	• Malnutrition–inflammation score	• Monthly
II. Measures that can be useful to confirm or extend the data obtained from the measures in category I	• Predialysis or stabilized serum prealbumin (transthyretin)	• As needed
	• Skinfold thickness	• As needed
	• Mid-arm muscle area, circumference, or diameter	• As needed
	• DXA for body composition assessment	• When feasible
III. Clinically useful measures, which, if low, might suggest the need for a more rigorous examination of protein-energy nutritional status	• Predialysis or stabilized serum	
	–Creatinine	• As needed
	–Urea nitrogen	• As needed
	–Cholesterol	• As needed
	• Creatinine index	

BMI, Body mass index; *DXA*, dual-energy X-ray absorptiometry; *NHANES*, National Health and Nutrition Examination Survey; *nPCR*, normalized protein catabolic rate; *nPNA*, normalized protein nitrogen appearance; *SGA*, subjective global assessment.

measurement of interdialytic weight gain (IDWG) and volume should be monitored. Because advanced CKD patients and chronic dialysis patients frequently have an abnormal body water content, the BMI may not be a good metric to estimate fat mass and its distribution unless the patient is very obese.

The threshold for BMI at which PEW can be diagnosed is not well defined. The International Society for Renal Nutritional and Metabolism (ISRNM) consensus paper recommended that a $\text{BMI} < 23\ \text{kg/m}^2$ can be used as an indicator for PEW in the dialysis population, although the relation between BMI and clinical outcome can be affected by race and ethnicity [29,43,44]. In many patients, a BMI of $23\ \text{kg/m}^2$ or lower may not indicate a pathological condition. In cross-sectional studies, anthropometric measurements (waist-to-hip ratio and skinfold thickness) have been found to be more accurate than BMI for identifying CKD patients with obesity. Mid-arm muscle circumference estimates muscle mass. The skinfold thicknesses at several areas in the body, including the triceps or biceps areas, can be used to estimate body fat. These quantitative anthropometric measurements (mid-arm muscle circumference and skinfold thickness) can be considered good indicators of PEW when they are below the 25th percentile of the values of well-nourished MHD patients [45]. For accuracy, anthropometry is best done by meticulous, experienced personnel with reliable equipment. Changes in dry weight has been correlated to relative risk of all cause death (Fig. 31.1).

The ISRNM panel recommends that a loss of 5% or more of edema-free body weight within 3 months or unintentional weight loss of 10% of edema-free body weight over 6 months indicates PEW independent of weight for height measures [29]. For routine overall assessment, the conventional version of SGA [47–51] and/or its new derivatives, such as the Malnutrition–Inflammation Score [52], should be evaluated twice-yearly. The Geriatric Nutritional Risk Index has been tested in MHD patients but remains a research tool at this time [53,54].

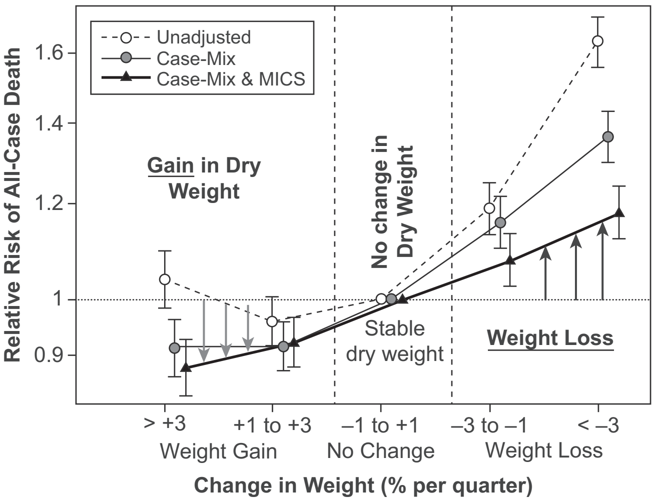

FIGURE 31.1 Association of change in dry weight over 6-months and 5-year mortality in 88,729 MHD patients [46]. *MHD*, Maintenance hemodialysis. *Source: Adapted from Kalantar-Zadeh K, Streja E, Kovesdy CP, et al. The obesity paradox and mortality associated with surrogates of body size and muscle mass in patients receiving hemodialysis. Mayo Clin Proc 2010;85(11):991–1001.*

The second category in the KDOQI nutritional assessment guidelines includes measures which help confirm or extend data obtained from the first category. Serum prealbumin (transthyretin) which, like serum albumin, is a negative acute phase protein has a strong association with mortality and hospitalization [55–57]. Dual-energy X-ray absorptiometry (DEXA) [58–60] is the recommended technique to assess body composition according to the KDOQI guidelines, although such alternative methods as bioelectrical impedance analysis (BIA) [61] and near infrared reactance (NIR) [62] can be very useful. DEXA was originally developed to measure bone density but has been adapted to measure fat and fat-free mass and soft tissue composition. DEXA provides minimal radiation exposure and can be completed within 5–15 minutes, which makes it suitable to use serially to monitor changes over time. BIA is performed by applying a small electrical current to a patient and measuring the resistance and reactance to the current. The ratio of resistance to reactance is used to derive total body mass. Total body water is derived from empirical equations. Phase angle measurement, which is a geometric derivative of the ratio of resistance to reactance, correlates strongly with serum albumin levels and anthropometric measurements of protein-energy status. Mushnick et al. showed that low phase angle measurements are associated with increased mortality [63] in chronic peritoneal dialysis (CPD) patients. BIA is best done (more reliably reproducible) within 2 hours after the end of a dialysis treatment in MHD patients [64]. But it has been recommended that BIA should not be done immediately after the completion of HD but rather about 30–60 minutes after completion. These energy beam–based methods of protein-energy assessment (DEXA, BIA, and NIR) have not yet been proven to improve clinical outcomes in MHD patients and may not be clinically superior to the simpler and less expensive tools as listed in category 1 in Table 31.1.

The third category in the KDOQI nutritional assessment guidelines includes measurements that are generally performed for other clinical purposes, but which if low values are found might suggest the need for a more rigorous examination of nutritional status. These measures include serum creatinine, urea and cholesterol concentrations, and the creatinine index (see Table 31.1). Recent studies have shown strong associations between serum TIBC, which is a reliable indicator of transferrin, and SGA and between both of these measures and clinical outcomes [65].

To be sure, many nonnutritional factors can affect the indicators in this third category. Serum TIBC is influenced by inflammation and, therefore, is not recommended by KDOQI as a measure of protein wasting. Apart from nutritional factors, either albumin synthesis or serum albumin is also affected by body losses of albumin, inflammation, acidosis, acute illness, and hydration status [66–68]. Serum albumin, prealbumin, and TIBC are negative acute phase reactants [68]. The dose of dialysis and magnitude of RRF can affect serum urea and creatinine. A number of epidemiological studies show that these common laboratory measures are strong predictors of hospitalization rates and mortality.

Dietary history, often obtained only for the previous 3 days, by a reliable and well-trained dietician or dietetic technician can also provide a valuable estimate of patient's intake of protein, energy, and other nutrients, particularly if these interviews are combined with a patient's diary of his/her food intake during this same period. Dietary diaries and interviews are time-consuming but can provide information of clinical value. Self-administered food frequency questionnaires (FFQs) may be used to estimate dietary intake in MHD patients. These questionnaires are not very precise and tend to underestimate food intake. Their main value may be to indicate what foods a patient may often, uncommonly, or never eat. FFQs are limited to epidemiological studies at this time.

The ISRNM has advanced a similar panel of assessment tools to screen for and diagnose PEW (Table 31.2). Biannual measurements of serum lipids are recommended because an increasing number of MHD patients, particularly those who have DM, have elevated serum lipids. In patients not taking cholesterol-lowering medications, very low serum cholesterol concentrations are a strong predictor of poor outcome in MHD patients [69,70].

TABLE 31.2 Additional recommended measures for monitoring nutritional and metabolic status of maintenance hemodialysis patients.

IV. Additional measures and tools	• Serum calcium, phosphorus, and Ca-P product	• Monthly
	• Serum potassium	• Monthly
	• Serum bicarbonate, anion gap	• Every 3 months
	• Serum TIBC or transferrin, iron saturation ratio	• Monthly
	• Serum ferritin	• Every 3 months
	• Lipid panel: total cholesterol, triglyceride, LDL and HDL cholesterol	• Every 6 months
	• Serum C–reactive protein[a]	• Every 3–6 months
	• Plasma total homocysteine	• Every 12 months

[a] *Other serum markers that may increase during inflammation include interleukin-6 (IL-6), IL-1β, and tumor necrosis factor alpha (TNF-α).*
HDL, High-density lipoprotein; *LDL*, low-density lipoprotein; *TIBC*, total iron-binding capacity.

As shown by Bergstrom et al. and others, elevated serum CRP levels will help identify patients who have inflammation [71]. CRP is an acute phase reactant that increases with inflammation and correlates negatively with serum albumin levels. To identify patients with inflammation, we recommend that serum CRP be measured every 3–4 months, preferably in every MHD patient. Serum CRP levels vary widely in MHD patients, and, therefore, one measurement of serum CRP may not be helpful. Serial measurements are of greater utility. Alternatively, if a patient has low serum albumin or prealbumin, the CRP may be measured to confirm whether an inflammatory state is present. Although both high and low plasma homocysteine levels are associated with poor outcomes in MHD patients, it is not a readily available measurement clinically, and it is not clear what measurements of homocysteine will add to the information that is obtained from the more commonly measured proinflammatory proteins [72–74].

Protein intake, nutritional status, urea kinetics, protein nitrogen appearance, and its relation to adequacy of dialysis

Measurement of protein intake in MHD patients can be based on the rise of urea nitrogen between two HD sessions, the urea generated during the latter HD session, and the 24-hour urinary excretion of urea, if the patient is not anuric. The urea nitrogen appearance and, hence, the PNA or PCR can be estimated from these urea kinetic measurements. PNA (PCR) reflects net protein degradation, which is the difference between the quantity of protein catabolized and the amount of protein synthesized per day. For a patient who is metabolically stable (i.e., no net protein accrual or loss), PNA (PCR) reflects the amount of his/her protein and amino acid intake each day. PNA or PCR is expressed as net grams of protein degraded per day. It is often normalized to the patient's body weight (nPNA or nPCR) and is expressed as grams protein/kg/day. nPNA (nPCR) can also be estimated from KT/V (index of urea removal during dialysis) and the average serum urea nitrogen (SUN).

Several studies reported a correlation between adequacy of dialysis, defined by KT/V_{urea}, and dietary protein intake as estimated by nPNA (nPCR) [75–77]. Many of these studies were not prospective or randomized, and, therefore, firm conclusions cannot be drawn. Underdialyzed patients are often uremic and anorexic and may have a low nPNA. Delivering a higher dose of dialysis to attain a higher KT/V often ameliorates appetite and increases protein intake [76–78]. A direct correlation between KT/V and PNA was shown in a prospective randomized study by Lindsay et al. [78]. When the KT/V was increased from 0.82 ± 0.19 (SD) to 1.32 ± 0.21 for 3 months, the PNA rose in the experimental group from an initial value of 0.81 ± 0.09 g/kg/day to 1.02 ± 0.15 ($P = .005$), whereas it did not change in the control group. These studies suggest that increasing the dose of HD from a Kt/V of 0.6 to 1.5–1.6 will increase the dietary protein intake in MHD patients. Harty et al. suggested that it is mathematical coupling that is the underlying reason for this effect, because the two parameters are obtained from the same plasma pre- and postdialysis measurements and are also both normalized to body size [79]. However, even when dialysis dose is not normalized to body size and protein intake is not estimated from urea kinetics, for example, if protein intake is estimated by dietary histories in continuous ambulatory peritoneal dialysis patients, several authors still report a significant correlation between dialysis dose and dietary protein intake [80–83].

Epidemiological studies suggest that a decline in protein intake (measured by nPNA or nPCR) may be associated with increased mortality in MHD patients

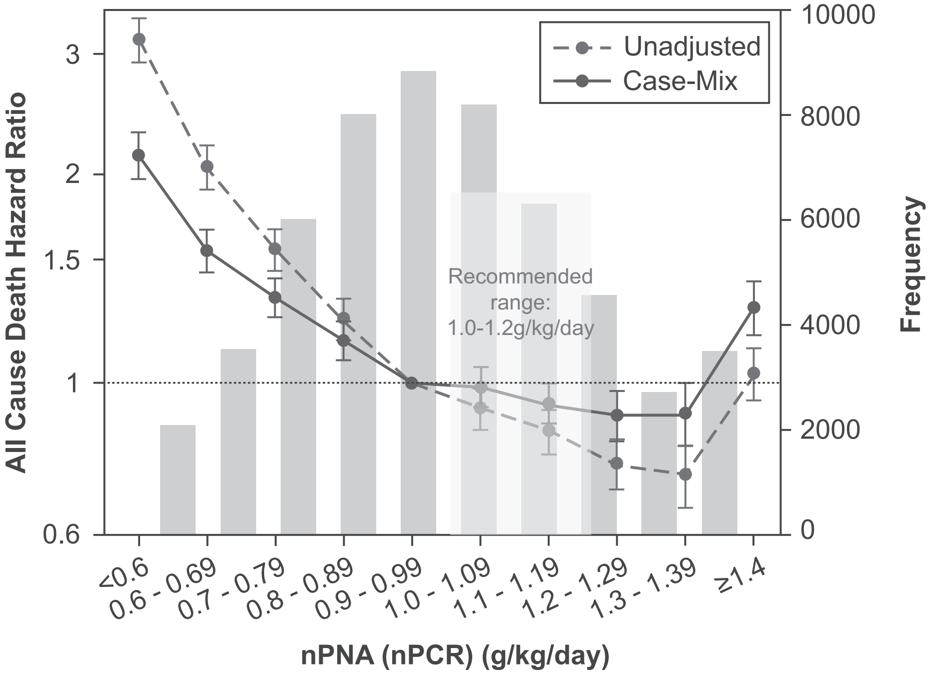

FIGURE 31.2 Association of estimated dietary protein intake (reflected by nPNA or nPCR) and 2-year mortality risk in 53,933 MHD patients. *MHD*, Maintenance hemodialysis; *nPCR*, normalized protein catabolic rate; *nPNA*, normalized protein nitrogen appearance. *Source: Adapted from Shinaberger CS, Kilpatrick RD, Regidor DL, et al. Longitudinal associations between dietary protein intake and survival in hemodialysis patients. Am J Kidney Dis 2006;48(1):37–49.*

[36,84]. In a longitudinal study of 53,933 MHD patients, the relation between nPNA and all-cause and cardiovascular mortality was examined over 2 years [36]. The greatest survival in the MHD patients was associated with an nPNA between 1.0 and 1.4 g/kg/day, whereas nPNA of <0.8 was associated with greater mortality (Fig. 31.2). Decreased protein intake, as measured with nPNA (range of nPNA was 0.8–1.2 g/kg/day) during the first 6 months of initiation of MHD, was associated with an incrementally greater risk of death over the subsequent 18 months [36]. Hence, an increase in nPNA was associated with trends toward reduced death risk. The Hemodialysis (HEMO) study on the other hand did not show a correlation between nPNA and mortality once serum creatinine and serum albumin levels were controlled for.

The correlation between Kt/V_{urea} and PNA is not precise [76–78]. Many patients with relatively high KT/V_{urea} (>1.5 for HD) have a very low PNA and, hence, reduced dietary protein intake. Independent of the uremic status of some patients, reduced protein intake can occur due to many different comorbid conditions. Patients with severe PEW often have reduced body weight and, therefore, for a given dialysis dose, tend to have higher Kt/V_{urea}, even though they may eat poorly [85]. There are currently no data as to what extent the Kt/V_{urea} affects dietary energy intake. Total 122 MHD patients who met the minimum requirements for dialysis adequacy ($Kt/V>1.20$) over the first 3 months of the observation period, independent of their RRF, showed a strong association between nPNA and subsequent hospitalization and mortality rates [86]. In this latter study the actual delivered Kt/V ranged from 1.23 to 2.71 (1.77 ± 0.34 SD) and nPNA ranged from 0.5 to 2.15 (1.13 ± 0.29) g/kg/day. The nPNA and Kt/V did not correlate significantly ($r=0.09$) except when the analysis was limited to $Kt/V<1.5$ ($r=0.54$) (see Fig. 31.3). Serum albumin levels and nPNA are the only variables that showed statistically significant correlations with hospitalization rates and mortality. These data suggest that protein intake tend to affect clinical outcomes in MHD patients, even among those who receive adequate doses of dialysis. The tight correlation between Kt/V and nPNA does not hold once Kt/V is >1.50. To confirm these conclusions, randomized prospective trials in MHD patients fed different protein intakes will be required.

It is recommended that MHD should receive a dialysis dose, measured by Kt/V, of at least 1.20 and the optimal goal is for an nPNA (nPCR) > 1.4 g/kg/day. In many dialysis facilities, it is difficult to attain a Kt/V of at least 1.20. The HEMO study failed to show an improvement in hospitalization or mortality with Kt/V (single-pool) values of 1.71 ± 0.11 SEM compared to 1.32 ± 0.09, but a number of epidemiological studies with very large sample sizes do show lower hospitalization rates with higher dialysis doses [87,88].

As indicated earlier, the use of nPNA or nPCR to estimate dietary protein intake requires that the patient is in neutral or near-neutral nitrogen balance. If a patient is in a net catabolic state, for example, a person with an inflammatory illness, the nPNA will usually overestimate dietary protein intake as these patients have an increased net generation of urea which will

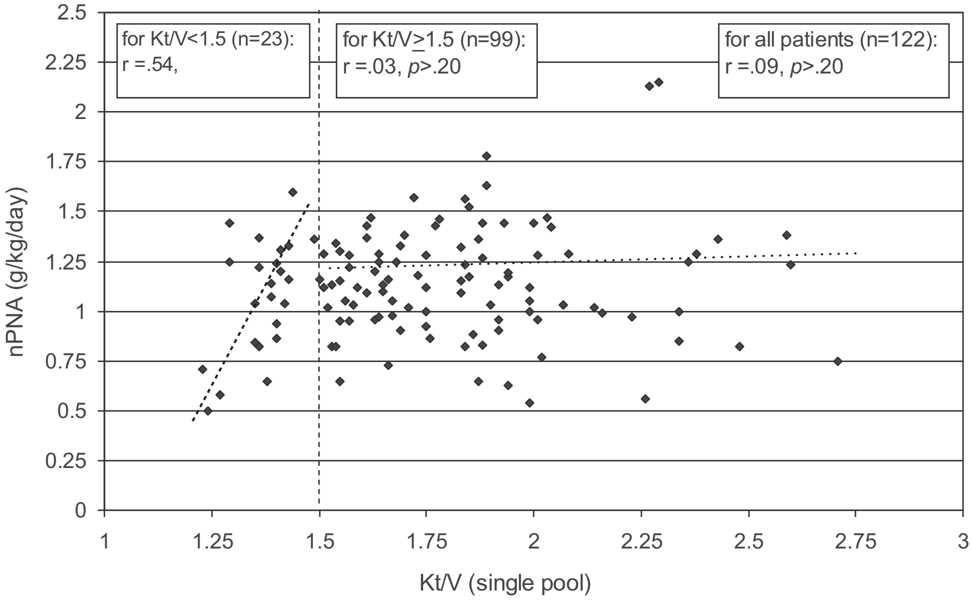

FIGURE 31.3 Exploring the association between nPNA and Kt/V_{sp} in 122 MHD patients with a Kt/V_{sp} value >1.20. No significant correlation existed between these two urea kinetic indices despite their known mathematical association ($r = 0.09$, $P > .20$). However, By dividing the patients into two distinct subgroups based on a Kt/V_{sp} cutoff of 1.50, there was a strong, significant correlation between Kt/V and nPNA for the lower Kt/V_{sp} values <1.50 ($r = 0.54$, $P < .001$), whereas there was essentially no correlation at higher Kt/V_{sp} values ($r = 0.03$, $P > .20$). *MHD*, Maintenance hemodialysis; *nPCR*, normalized protein catabolic rate; *nPNA*, normalized protein nitrogen appearance. *Source: Reprinted with permission from Kalantar-Zadeh K, Supasyndh O, Lehn RS, McAllister CJ, Kopple JD. Normalized protein nitrogen appearance is correlated with hospitalization and mortality in hemodialysis patients with Kt/V greater than 1.20. J Ren Nutr 2003;13(1):15–25.*

increase nPNA (nPCR). On the other hand, nPNA may underestimate protein intake in patients with large protein losses (e.g., patients with the nephrotic syndrome or CPD patients with peritonitis) or in anabolic patients; for example, women in the last trimester of pregnancy, patients recovering from acute infection, and children with rapid growth.

PNA may change rather quickly after a shift in dietary protein intake or in the patient's catabolic state, and under these conditions, PNA may not reflect the patient's usual protein intake. Since body weight is in the denominator of the units for nPNA or nPCR (g/kg/day), the nPNA (nPCR) may be misleading in patients who are obese, have PEW, or are elderly and debilitated [89]. To accurately assess protein intake, it, therefore, has been proposed that nPCR (nPNA) should be normalized, preferably to some parameter related to the body weight of a normal person of the same height, age, and sex as the patient.

Utility of the predialysis serum urea nitrogen level to estimate protein intake

The SUN concentration at the beginning of a HD session (predialysis) can often be used to provide a rough estimate of the adequacy of an MHD patient's protein intake. The predialysis SUN reflects the balance between the removal of urea (by dialysis or RRF) and net urea generation from protein catabolism. In a clinically stable person who is in protein balance, urea generation is largely determined by protein intake. There is a relatively small amount of urea recycling that occurs in the gastrointestinal tract, and unless the patient has a substantial acid load, the amount of amino nitrogen from degraded protein that is converted into ammonium by the kidney is small. Therefore when using the predialysis SUN to estimate protein intake, these latter two processes can largely be ignored, especially in advanced kidney failure where renal ammonium production is limited or absent. Thus an MHD patient with minimal RRF who is well dialyzed and has a sufficient protein intake (e.g., about 1.2-g protein/kg/day) should have a predialysis SUN of roughly around 90–100 mg/dL. A predialysis SUN of about 60 mg/dL or lower in a normally dialyzed patient with little or no RRF will indicate an inadequate protein intake, whereas a predialysis SUN of 100 mg/dL in a patient who is poorly dialyzed may also be consistent with a low-protein intake. On the other hand, a patient with substantial RRF (e.g., with a urine output of 300 mL/day or greater) can have a lower predialysis SUN with an adequate protein intake. Thus evaluating a combination of the predialysis SUN and the patient's clinical/catabolic status, adequacy of dialysis treatments and level of RRF may enable the physician to make a rough guess as to the adequacy of the patient's daily protein intake.

Acidemia and protein wasting

Experimental evidence indicates that acidemia enhances protein catabolism [15,90–97]. In rats, acidemia increases the activity of branched-chain ketoacid dehydrogenase which is an enzyme involved in the catabolism of branched-chain amino acids [90]. Bergstrom et al. reported that there is a linear correlation between predialysis plasma bicarbonate levels and muscle-free valine in MHD patients [96]. This suggests that acidemia can enhance the degradation of at least some amino acids. Acidemia can increase protein catabolism and induce negative nitrogen balance [92]. This proteolysis induced by acidemia in skeletal muscle is due to enhanced activity of the ATP-dependent ubiquitin proteasome pathway [93–95]. Interestingly, even normal individuals who develop metabolic acidemia by ingesting ammonium chloride for several days reduce synthesis of albumin and develop negative nitrogen balance [98].

Acidemia in MHD patients may be common as evidenced by the frequent finding of low predialysis serum bicarbonate levels [10–12,99]. It is important to note that low serum bicarbonate is not definitive proof that acidemia exists. Direct pH measurements are a more accurate way to conclusively demonstrate acidemia. Published literature strongly suggests that acidemia is harmful, and, therefore, it is strongly recommend that bicarbonate supplements be given to maintain serum bicarbonate of 24–26 mEq/L (Clinical Practice Guideline 6.1.3) throughout the interdialytic interval unless it is determined that the low serum bicarbonate level is associated with normal arterial blood pH in a given patient [14]. Our experience indicates that the MHD patients most likely to develop acidemia during the interdialytic interval are those with substantial RRF, presumably because these individuals may have substantial urinary bicarbonate losses.

Goals of nutritional management in maintenance hemodialysis patients

There are four goals for dietary therapy or nutritional intervention: (1) to achieve and maintain good nutritional and metabolic status, (2) to prevent or ameliorate uremic toxicity, (3) to prevent or treat hyperparathyroidism and renal osteodystrophy, and (4) to prevent or retard the development of cardiovascular disease. It is a challenge for many MHD patients to adhere to a special diet with its multiple restrictions. MHD patients often eat too little rather than too much. Due to these challenges, it is important to educate patients on the principles of dietary therapy, including the rational, goals implementation of such therapy. Nutritional training also includes educating patients to read food labels, so they can ascertain the nutrient content of foods, and to assemble foods into meal patterns that are consistent with their dietary prescription. Even patients who have no interest in dietary management may benefit from nutritional training for several reasons. First, patients may decide to follow dietary therapy after they receive the education. Second, even if they adhere poorly to the prescribed diet, it may still provide some health benefits. Third, nutrition education may help motivate patients to not deviate further from a healthy nutrient intake. Nutritional training may be especially helpful if the patient's age and emotional or physical stresses are contributing to poor dietary compliance.

Dietary nutrient requirements

Dietary protein requirements

There are no prospective randomized clinical trials examining the morbidity and mortality of MHD patients assigned to different levels of dietary protein intake as the independent variable (see Table 31.3). Several prospective studies compared the effects of dietary protein intake on the nutritional status of MHD patients. Most of these trials were conducted in hospital research wards with relatively small numbers of patients [100–102]. The studies that addressed protein requirements in HD patients were usually carried out several years ago and used dialyzers with lower solute clearances than those that are currently in use [101,102]. Other studies conducted retrospective analyses of larger numbers of patients that examined the relationship between dietary protein intake, assessed from nPNA, and morbidity and mortality [36,84,103,104].

The KDOQI guidelines on nutrition in chronic renal failure recommend a dietary protein intake of 1.0–1.2 g/kg body weight/day in stable MHD patients [14]. At least 50% of this protein intake should be of high biological value that ensures adequate intake of essential amino acids. These recommendations are based on the level of protein intake that for the great majority of clinically stable MHD patients (about 97%) should maintain neutral or positive nitrogen balance and lead to maintenance or improvement of nutritional or protein markers such as serum albumin. This is the same reasoning that has led to the development of the Recommended Daily Allowances for normal people by the National Academy of Medicine. It follows from this reasoning that if 1.2-g protein/kg/day will

TABLE 31.3 Recommended dietary nutrient intake for adult patients undergoing maintenance hemodialysis.

Macronutrients and fiber	
DPI[a]	1.2 g/kg body weight/day for clinically stable MHD patients. >1.2–1.3 g/kg/day for patients who are acutely ill or have more severe protein-energy wasting
DEI[b]	35 kcal/kg body weight/day for those who are <60 years of age and 30–35 kcal/kg body weight/day for individuals 60 years or older
Fat intake[c]	30% of total energy intake
Total fat[c, d]	30% of total energy intake
Saturated fat[c]	Up to 10% of total energy intake
Polyunsaturated–saturated fatty acids[c]	Up to 10% of total calories
Monounsaturated fatty acids[c]	Up to 20% of total calories
Carbohydrate[c, d, e]	Rest of nonprotein calories
Total fiber[f]	20–25 g/day
Minerals and water (range of intake)	
Sodium	750–2000 mg/day
Potassium	up to 70–80 mEq/day
Phosphorus[g]	10–17 mg/kg/day
Calcium[h]	<1000 mg/day
Magnesium	200–300 mg/day
Iron[I]	See text
Zinc	15 mg/day
Water	Usually 750–1500 mL/day
Vitamins (including dietary supplements)	
Vitamin B1 (thiamin)	1.1–1.2 mg/day
Vitamin B2 (riboflavin)	1.1–1.3 mg/day
Pantothenic acid	5 mg/day
Biotin	30 μg/day
Niacin	14–16 mg/day
Vitamin B6	10 mg/day of pyridoxine hydrochloride; 8.2 mg of free pyridoxine
Vitamin B_{12}	2.4 μg/day
Vitamin C	75–90 mg/day
Folic acid[j]	1–10 mg/day
Vitamin A	See text
Vitamin D	See text
Vitamin E[k]	15 IU
Vitamin K[l]	See text

(*Continued*)

TABLE 31.3 (Continued)

[a] *According to KDOQI guidelines.*

[b] *Refers to percent of total energy intake (diet plus dialysate).*

[c] *Although atherosclerotic vascular disease constitutes a common and serious problem for MHD patients, these recommendations regarding dietary fat and carbohydrate are often difficult to adhere to. Moreover, there is no prospective interventional study that has examined whether these modifications of dietary fat and carbohydrate reduce morbidity or increase survival in CKD or MHD patients, although, reasonably, these modifications would seem to be beneficial. They are strongly recommended only if patients adhere closely to more critical aspects of the diet (e.g., sodium, water, potassium, phosphorus, protein, and energy intakes) and have expressed a particular interest in these modifications or have a specific disorder that may respond to their medications.*

[d] *Refers to percent of total energy intake; if triglyceride levels are very high, the percentage of fat in the diet may be increased to about 35% of total calories; otherwise, 25%–30% of total calories is preferable. Intake of fatty acids should be kept low because they raise LDL cholesterol (see text).*

[e] *Should be primarily complex carbohydrates.*

[f] *Less critical to adhere to for the typical MHD patient.*

[g] *Phosphate binders (aluminum carbonate or hydroxide, or calcium carbonate, or acetate) often are needed to maintain normal serum phosphorus levels.*

[h] *These calcium intakes are commonly ingested because of the use of calcium binders of phosphate. Excess calcium intake must be avoided (see text).*

[i] *Iron requirements vary according to the dose of administered erythropoietin.*

[j] *Folic acid 1 mg/day should be routine, but up to 10 mg/day may be given to reduce elevated plasma homocysteine levels.*

[k] *Vitamin E, 300 or 800 IU/day, may be given to reduce oxidative stress and prevent cardiovascular disease, but the value of these supplements is controversial (see text and Chapter 20: Nutritional Management of Sodium, Chloride and Water in Kidney Disease and Kidney Failure).*

[l] *Vitamin K supplements may be needed for patients who are not eating and who receive antibiotics.*

CKD, Chronic kidney disease; *DEI*, daily energy intake; *DPI*, dietary protein intake; *KDOQI*, Kidney Foundation Kidney Disease Outcomes Quality Initiative; *LDL*, low-density lipoprotein; *MHD*, maintenance hemodialysis.

maintain protein balance for about 97% of clinically stable MHD patients, many such patients will maintain protein balance with a lower protein intake. The problem is that when prescribing the diet, it usually is not possible to know which MHD patients can maintain protein balance with lower protein intakes. Clearly more research is needed to address the protein needs of MHD patients. The following is a review of the research that has been published so far.

Kopple et al. reported results of nitrogen balance studies conducted on three MHD patients admitted to a metabolic unit [102]. These patients were receiving MHD for 11 hours twice weekly using a Kiil dialyzer. For about 3 weeks each, two separate isocaloric diets were given to these patients that provided 0.75-g protein or 1.25 g of primarily high biological value protein/kg/day. Nitrogen balance was negative or neutral with 0.75-g protein/kg/day diet (adjusted to unmeasured nitrogen losses) and strongly positive with 1.25-g protein/kg/day. Kopple et al. then carried out a study on 23 outpatient MHD patients assigned to receive either diet while they underwent with HD twice weekly for 10–12 hours with Kiil dialyzers. The estimated protein intake was about 0.8- to 0.9-g protein/kg/day in patients assigned to the low-protein diet and about 1.1- to 1.2-g protein/kg/day in those assigned the high-protein diet. Those patients who received the low-protein diet had only a small improvement in their serum albumin and body weight. The high-protein group had a statistically significant improvement in serum albumin and body weight. Borah et al. studied five MHD patients given either 0.50- or 1.44-g protein/kg/day under metabolic balance conditions [18]. This diet was fed for only 7 days. The investigators concluded that high-protein diets resulted in neutral or positive nitrogen balance and low-protein diets caused negative nitrogen balance.

Ginn and coworkers performed nitrogen balance studies on four MHD patients undergoing MHD twice weekly [101]. Two of these four MHD patients were fed 18-g protein/day and were in severe negative nitrogen balance. The other two patients were fed higher protein diets. Their nitrogen balance was positive when they ingested 0.8 g/kg/day of primarily high biological value protein. Interestingly, nitrogen balance was sometimes negative with the higher protein diets when the protein was of low biological value. The positive nitrogen balance observed in MHD patients who received low-protein diets (i.e., 0.8-g protein/kg/day) may have been because these patients were severely malnourished, were receiving only twice-weekly dialysis, and this diet might have provided more protein than the patients had previously been eating. Shinaberger and Ginn reported that 10 MHD patients who ingested 0.75 g/kg/day showed improvement in nutritional status [105]. Most of these patients were malnourished and had probably been eating poorly before the study. Since these patients received only twice-weekly dialysis, this may have limited both the amino acid, peptide, and protein losses during HD and the inflammatory, catabolic effects of HD (see earlier). These factors may explain the anabolic response with the low-protein diet the patients ingested. Also, the protein diet actually consumed by the patients probably exceeded 0.75 g/kg/day.

Slomowitz and coworkers reported metabolic studies conducted in six MHD patients [106]. The patients lived in a clinical research ward for 63–65 days and received HD three times weekly using Cuprophan or cellulose acetate dialyzers. Although this study was conducted to assess dietary energy needs, it also gave information on the protein needs of MHD patients. These patients were fed a constant protein diet throughout the study that provided 1.13 ± 0.02 SEM g protein/day. Patients were fed three different energy intakes (25, 35, and 45 kcal/kg/day) in random order for 21–23 days each. Of the six patients the number that were in neutral or positive nitrogen balance with the 25, 35, and 45 kcal/kg/day intakes were one (possibly), four, and six individuals, respectively. Since the usual energy intake of clinically stable MHD patients is <30 kcal/kg/day [107], these results suggest that for many of the MHD patients who ingest about 25 or even 35 kcal/kg/day, a dietary protein intake of 1.1 g/kg/day may not be sufficient to maintain protein balance. The nitrogen balance data with energy intake of 35 kcal/kg/day with protein intake of 1.1 ± 0.02 SEM g/kg/day are shown in Table 31.4. These

TABLE 31.4 Nitrogen balance data in six maintenance hemodialysis patients[a] ingesting a diet providing about 1.13-g protein/kg/day and about 35 kcal/kg/day.

Gender	Age (years)	Body weight (kg)	Energy intake (per kg) Actual body weight (kcal/kg/day)	Duration of study (days)	Stable period (days)[b]	Nitrogen intake[c] (g/day)	Urine nitrogen	Fecal nitrogen	Dialysate nitrogen	Total Nitrogen output[d]	Adjusted Nitrogen balance[e]
Female	61	60.6	35.8	21	14	11.0	0.78	0.68	7.40	8.86	+2.09
Female	64	73.6	31.3	21	7	11.4	0.20	1.15	9.15	10.50	+0.68
Male	46	73.3	35.6	21	14	13.4	0.84	0.99	10.52	12.35	+1.02
Male	43	58	45.4	21	7	14.0	0	1.60	12.07	13.67	+0.06
Male	24	51.4	41.2	21	14	11.2	0.12	1.14	8.80	10.06	+0.61
Male	42	70.5	34.5	21	7	12.8	0	1.70	11.90	13.75	−1.02
Mean	46.7	64.6	37.3	21	10.5	12.18	0.32	1.21	9.97	11.53	+0.57
SEM	59	3.8	2.1	0	1.6	0.53	0.16	0.16	0.75	0.83	0.42

[a] *Balance data were obtained during the stable period, which is the time after patients had stabilized or equilibrated on each diet.*

[b] *Refers to the period in which nitrogen balance had equilibrated and was no longer changing.*

[c] *Refers to the measured nitrogen intake minus the nitrogen content of rejected or vomited food.*

[d] *Sum of urine, fecal, and dialysate nitrogen.*

[e] *Indicates nitrogen balance adjusted for changes in body urea nitrogen but not unmeasured losses from skin, nails, or hair, growth, respiration, or blood drawing.*

Printed with permission from Slomowitz LA, Monteon FJ, Grosvenor M, Laidlaw SA, Kopple JD. Effect of energy intake on nutritional status in maintenance hemodialysis patients. Kidney Int 1989;35(2):704–11.

balance studies suggest that some clinically stable MHD patients will not maintain protein balance with dietary protein intake of 1.1 g/kg/day and energy intakes providing 25 or 35 kcal/kg/day.

The KDOQI recommendations suggest that in patients who are metabolically stable, a dietary protein intake of 1.0–1.2 g/kg ideal body weight/day maintains stable nutritional status [14]. The current guidelines may be considered safe and justified until more data are available. The methods for calculating ideal body weight or even the use of this term are not conclusively validated in MHD patients.

Retrospective and observational studies concerning dietary protein requirements

Data from retrospective and observational studies support the previous recommendation of 1.0- to 1.2-g protein/kg/day for MHD patients. Data from the National Cooperative Dialysis Study suggest that a dietary protein intake <0.8 g/kg/day (estimated by nPNA) is associated with increased morbidity [108]. These patients were randomized to a specific midweek predialysis SUN, and, therefore, the patients received a range of dialysis times and doses of dialysis. Therefore it is difficult to arrive at a firm conclusion that the morbidity was due to lower nutritional intake per se and not due to decreased dialysis dose. It should also be emphasized that due to the unmeasured nitrogen losses through respiration, skin, etc., in clinically stable people, the nPNA (nPCR) underestimates the dietary protein intake unless an adjustment factor is added [109].

Acchiardo et al., in a retrospective study, examined the relationship between dietary protein intake determined by nPCR and mortality, frequency of hospitalizations, and number of hospital days in 98 nondiabetic MHD patients followed for a 12-month period [103]. Based on their nPNA, patients were divided into four groups (nPNA of 0.63, 0.93, 1.02, and 1.2 g/kg/day). The frequency of hospitalization and mortality were inversely correlated with dietary protein intake. With an nPNA of 0.63 g/kg/day, the hospitalization rate and mortality was particularly likely to be elevated. It is not known whether an nPNA higher than 1.2 g/kg/day would be associated with a further reduce morbidity and mortality. Again, it should be recognized that the nPNA (nPCR) underestimates protein intake in clinically stable individuals unless a mathematical adjustment is made [109]. These data should be qualified because patients ingesting lower amounts of protein were probably more likely to be acutely or chronically ill, and this may have increased their risk for morbid events and mortality.

Although some investigators report that some MHD patients are in nitrogen balance at protein intake of 0.7 g/kg/day, these data, if typical for these patients, indicate that they are outliers [102,110]. Our analysis of the dietary protein data is in agreement with the KDOQI guidelines that a protein intake of 1.0–1.2 g/kg ideal body weight/day is much more likely to maintain healthy body protein mass and nutritional status in clinically stable MHD patients [14]. However, as indicated in the foregoing discussion, some stable MHD patients do not seem to maintain protein balance with an intake of 1.0 or 1.1 g/kg/day. Hence, in the absence of a specific contraindication (e.g., liver failure), it may be preferable to encourage MHD patients to ingest closer to 1.2-g protein/kg/day. If a patient is ingesting a lower protein intake and shows no evidence of PEW, it may be reasonable to not try to increase his/her dietary protein. On the other hand, a clinically stable MHD patient who shows signs of developing PEW or who has PEW and who is ingesting 1.1-g protein/kg/day or less, may be encouraged to increase his protein intake to 1.2- or 1.3-g protein/kg/day [111]. A retrospective study that demonstrated a positive association between dietary protein intake and survival in MHD patients supports the potential benefit of even a slightly higher protein intake in these individuals [36].

Dietary energy requirements

Epidemiological studies in MHD patients suggest that suboptimal energy intake is even more common than inadequate protein intake [104,107,112–116]. Even in the HEMO study, where energy intake was closely monitored by renal dieticians, the average energy intake was 22.8 ± 8.8 SD kcal/kg adjusted body weight/day [107,117,118]. The low energy intakes of MHD patients do not reflect a decrease in energy requirements [119,120]. Studies indicate that basal metabolic energy expenditure in MHD patients during resting conditions is normal [121] or possibly slightly increased. Resting basal energy expenditure was compared in one study between 12 normal subjects and 16 MHD patients [119]. In the normal subjects, it was 0.94 ± 0.24 and in the MHD patients was 0.97 ± 0.1 kcal/min/1.73 m^2 [119].

Schneeweiss et al. performed indirect calorimetry on 24 normal adults and 86 subjects with CKD in different stages; 25 of the 86 CKD patients were receiving MHD [122]. The resting energy expenditure of the MHD patients was 1.03 ± 0.04 SEM kcal/min/1.73 m^2 in MHD patients and was 0.96 ± 0.02 in the control subjects. This difference in energy expenditure between the MHD patients and normal adults was not significantly different. Neyra et al. measured resting energy expenditure by indirect calorimetry using a metabolic chamber (whole room indirect calorimeter) in 15 nondialyzed patients with advanced CKD, 15 MHD patients, and 10 CPD patients who had undergone 12 hours of fasting [123]. Energy expenditure was measured in the MHD patients on days when they were not receiving dialysis. Resting energy expenditure, adjusted for fat-free mass, was similar in the MHD and CPD patients and was significantly greater in each of these groups than in the nondialyzed advanced CKD patients ($P < .05$). Resting energy expenditure in the patient groups was about 10%–20% higher than the predicted values for normal people. However, the normal values for energy expenditure were calculated and not measured.

In contrast to these findings, Monteon et al. found that resting energy expenditure, measured by indirect calorimetry, was similar in nondialyzed advanced CKD patients, MHD patients, and normal control individuals [119]. Energy expenditure in these three groups also did not differ from each other when they were sitting quietly, undergoing a specified amount of physical exertion, or after ingesting the same, defined meal [119]. Energy expenditure was reported to be increased in MHD patients during an HD session [123]. These patients were fed before their HD, and their increased energy expenditure may have been due to the specific dynamic action of foods. Energy expenditure may be increased in MHD patients who have increased serum CRP levels.

Slomowitz et al. showed in the previously described study that in six clinically stable MHD patients who were fed, in a research ward, a constant protein diet that provided, in random order, 25, 35, or 45 kcal/kg/day, both changes in their body weight and their nitrogen balances correlated directly with the dietary energy intake [106]. The average nitrogen balance was neutral when patients ingested 35 kcal/kg/day, although not every patient was in neutral or positive nitrogen balance.

The usual energy intake of MHD patients, as reported in many studies, seems to be inadequate in comparison to their needs, since their skinfold thicknesses, and, hence body fat, are low. The exception to this is that patients who begin MHD therapy obese tend to remain obese during the course of their treatment. There is also an altered risk factor pattern between obesity and survival in MHD patients. MHD patients who have larger body mass tend to survive longer [70,124–126].

The KDOQI guidelines recommend that daily energy intake should be 35 kcal/kg/day for MHD patients who are <60 years of age and 30–35 kcal/kg/day for those who are 60 years or older [14]. This recommendation is based on the following findings: (1) the energy expenditure of MHD patients is similar or, at most, slightly increased in comparison to that of normal healthy individuals who are resting or performing mild physical activity. (2) Metabolic balance studies of MHD patients indicate that a total daily energy intake of about 35 kcal/kg/day induces neutral nitrogen balance in most MHD patients and is adequate to maintain serum albumin and anthropometric indices. (3) Individuals who are 60 years or older tend to be more sedentary and, hence, expend less energy. Therefore a slightly lower total energy intake of 30–35 kcal/kg/day should be sufficient. These recommendations are similar to the recommended dietary allowances for sedentary healthy adults by the Food and Nutrition Board of the National Research Council (Food and Nutrition Board; Dietary Reference Intakes: National Academy Press: Washington DC, 2001).

Lipids and hemodialysis

Management of lipid disorders has the theoretical potential to change cardiovascular morbidity and mortality in MHD patients. Cardiovascular mortality accounts for half of the mortality in chronic dialysis patients with about one-quarter of total deaths attributable to sudden cardiac death [127–130]. Dyslipidemia is more prevalent in ESRD patients than in the general population [131,132].

In the general population, elevated serum total cholesterol and low-density lipoprotein (LDL) cholesterol levels are associated with increased mortality. In a striking example of the altered risk factor patterns that occur in chronic dialysis patients, the low serum total cholesterol levels (below 200–250 mg/dL) and decreased (LDL) levels that may occur in MHD patients are associated with increased mortality [133,134]. This altered association has been attributed to inflammation which can both lower serum LDL and total cholesterol and increase mortality.

Hypertriglyceridemia and low serum high-density lipoprotein (HDL) concentrations often occur in MHD patients [135,136]. Very LDL is usually increased, but LDL and total cholesterol levels are normal or reduced compared to the general population [137–139]. Increased serum apolipoprotein B containing triglyceride-rich lipoprotein particles, such as lipoprotein Bc, and elevated lipoprotein(a) [LP(a)], are also independently associated with increased risk of myocardial infarction and death in patients with renal failure [140–143]. Reduced clearance of serum LP(a) is a cause of elevated serum levels in advanced CKD and ESRD patients. LP(a) can inhibit fibrinolysis, leading to thrombosis and atherosclerosis. Postprandial clearance of chylomicron remnants is reported to be defective in MHD patients [144,145]. Type 4 hyperlipidemia is frequently seen in ESRD patients [140−144,146].

All fractions of serum HDL cholesterol are often decreased, possibly due to reduced lecithin−cholesterol acyltransferase activity. Serum HDL-3 is not affected. Serum HDL-3 is not one of the major risk factors for reduced adverse cardiovascular events. An elevated serum HDL-2 on the other hand has a strong association with lower cardiovascular morbidity and mortality, and HDL-2 is significantly reduced in ESRD patients. The antiatherogenic HDL-associated Apo A1 and Apo A2 are also reduced in ESRD patients. Lipoprotein lipase activities in serum and liver are decreased. Serum levels of oxidized lipids and thiobarbituric acid reactive substances are elevated in CKD and MHD patients. Schletter et al. report that lipid oxidation is not increased in MHD patients [147], although other researchers have hypothesized that it may be increased.

MHD patients with hypertriglyceridemia should be evaluated for systemic causes of this disorder, such as hypothyroidism and DM. Hypertriglyceridemia is more common than hypercholesterolemia in MHD patients. When the serum triglyceride concentrations are 1.25−1.50 times the upper limit of normal values, dietary interventions may be used and are effective. Dietary therapy includes decreased intake of ethanol, purified sugars, and saturated fat. If after institution of these interventions, serum triglycerides are not reduced sufficiently (i.e., after a 10-hour fast serum triglycerides remain >500 mg/dL), medications can be considered. Medical therapy can be given concurrently with lipid-lowering diets [148−150]. Gemfibrozil and such fibric acid derivatives as clofibrate are effective medications to reduce serum triglyceride levels. According to the KDIGO guidelines, there is very little evidence that the use of fibrates in CKD patients is clinically beneficial, unless serum triglyceride levels are >1000 mg/dL [151]. Adverse effects of these medications include rhabdomyolysis, and a dose reduction should be made for MHD patients [152−155].

There is currently no consensus as to the optimal lipid composition of the diet for MHD patients. The National Cholesterol Education Program Expert Panel has recommended the Therapeutic Lifestyle Changes (TLC) diet for all individuals with serum LDL cholesterol of 100−125 mg/dL or greater or serum triglycerides higher than 180 mg/dL [156]. Table 31.5 shows the nutrient composition of the TLC diet. Its key features are (1) reduced intake of saturated fats (to <7% of total calories) and cholesterol (to <200 mg/day). (2) Sources of total calories in the diet should include up to 10% from polyunsaturated fats, up to 20% from monounsaturated fats, 25%−35% from all fat sources, and the rest from protein and carbohydrates. Dietary protein in the TLC diet should provide 1.20-g protein/kg/day, and dietary carbohydrate should be modified accordingly to maintain the desirable energy intake. (3) Consider therapeutic options for lowering serum LDL by ingesting plant sterols (2 g/day). (4) Attainment and maintenance of desirable body weight and expend at least about 200 kcal/day in physical activity.

TABLE 31.5 Nutrient composition of the therapeutic lifestyle changes diet.

Nutrient	Recommended intake
Saturated fat[a]	<7% of total calories
Polyunsaturated fat	Up to 10% of total calories
Monounsaturated fat	Up to 20% of total calories
Total fat	25%−35% of total calories
Carbohydrate[b, c]	50%−60% of total calories
Fiber	20−30 g/d
Protein[c]	Approximately 15% of total calories
Cholesterol	<200 mg/d
Total calories[d]	Balance energy intake and expenditure to maintain desirable body weight/prevent weight gain

[a] Trans *fatty acids are another LDL-raising fat that should be kept at a low intake.*
[b] *Carbohydrates should be derived predominantly from foods rich in complex carbohydrates, including grains, especially whole grains, fruits, and vegetables.*
[c] *Dietary content of protein and, hence carbohydrate, should be modified according to the specific needs of the MHD (i.e., 1.20-g protein/kg/day) (see text).*
[d] *Daily energy expenditure should include at least moderate physical activity (contributing approximately 200 kcal/day).*
LDL, Low-density lipoprotein; *MHD*, maintenance hemodialysis.
From Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults. Executive summary of the third report of the National Cholesterol Education Program (NCEP) expert panel on detection, evaluation and treatment of high blood cholesterol in adults: adult treatment panel III. JAMA 2001;285:2486−97.

KDIGO and KDOQI clinical practice guidelines do not recommend starting a statin medication (3-hydroxy-3-methyl-glutaryl (HMG) coenzyme A inhibitor) or the combination of a statin with ezetimibe, an intestinal cholesterol absorption inhibitor, in MHD patients because there is no clear evidence that decreasing serum LDL cholesterol reduces morbidity or all-cause mortality in these individuals. One hypothesis to explain this lack of benefit in all-cause mortality is that sudden cardiac death in MHD patients is not related to obstructive atherosclerotic lesions that can be modified by statins; the sudden death in these patients might be related to heart failure and/or arrhythmias due to eccentric and or concentric cardiac hypertrophy [157]. Another possibility is that the statin therapy was studied for periods of about 5 years in these clinical trials, whereas the process of atherosclerosis had begun many years earlier; therefore the statin treatment might have been inaugurated too late to be very effective.

It is reasonable to recommend that if a patient is already taking statins before the initiation of MHD, the patients should continue taking statins. This latter recommendation is mostly based on the SHARP trial that examined 2141 patients with CKD that progressed to requiring dialysis [158]. The patients in this study who were taking simvastatin, 20 mg/day, and ezetimibe, 10 mg/day, had a significant reduction in major cardiovascular events.

Long-chain omega-3 polyunsaturated fatty acids

The KDOQI guidelines recommend that MHD patients can be prescribed 1.3–4.0 g/day long-chain omega-3 polyunsaturated fatty acids (LC $n-3$ PUFA) to reduce serum triglycerides, reduce serum LDL cholesterol, and increase serum HDL levels [14]. The KDOQI guidelines also suggest that LC $n-3$ PUFA, including those derived from fish or flax seed and other oils, should not be routinely prescribed to lower risk of mortality or cardiovascular mortality [14]. We agree with this suggestion. These should be prescribed only to reduce elevated triglycerides, reduce LDL cholesterol, and increase serum HDL levels.

Sodium and water

Interdialytic weight gain and its relation to salt and water intake

Management and monitoring of IDWG is critical to preventing and/or reducing the risk of volume related hypertension, left ventricular hypertrophy, congestive heart failure, and right heart failure [159,160]. Dietary counseling to avoid high salt and fluid intake is, therefore, critical to limit large IDWG in MHD patients. Fluid removal >13 mL/kg/hour during HD in MHD patients has been linked to such adverse events as intradialytic hypotension and myocardial stunning [161–164]. It is, therefore, critical for patients to limit their salt and water intake for as long as they are receiving MHD to avoid cardiovascular complications.

Reduction or complete avoidance of antihypertensive medications can be achieved at least in some patients with diligent restriction of salt and water intake during the interdialytic period. Shaldon and Tomson have reported medication-free blood pressure control with aggressive salt and fluid restriction. The KDOQI guidelines recommend both salt and water restriction, since restriction of only water intake will lead to increased serum osmolality which will stimulate thirst-related water intake [14]. MHD with longer than 4-hour HD sessions or conducted more frequently than thrice weekly are other effective ways to attain good blood pressure control, often with the need for only little or no antihypertensive medications.

Salt (sodium chloride) intake should be limited to no >5 g/day (2 g/day of sodium). One study described the average daily salt intake in MHD patients in the United States to be between 7.9 and 14.1 g/day [165]. To reduce dietary salt intake, almost all people must make substantial changes from their old habits of food intake and cooking—for the people who prepare the food. These changes are emotionally wrenching for many people. To attain these goals, significant effort must be directed toward dietary counseling. Dietitians must be supported in this effort by the other members of the health-care team (i.e., doctors, nurses, social workers, technicians, and unit administrators).

Some medications are sources of sodium intake. Examples of this include combined analgesics in effervescent form. An example is cocodamol, a combination of codeine and paracetamol, used mostly in Europe. This preparation contains 19.1 mmol (438 mg) of sodium in each tablet. If a patient takes six to eight of these tablets, the excess sodium intake can cause increased thirst and, as a result, may result in approximately an 800-mL increase in water intake per day to maintain a normal plasma sodium concentration.

Strategies used in selected studies to reduce salt and water intake

Sevick et al. reported that nutritional counseling, social cognitive theory-based behavioral counseling for 16 weeks failed to reduced dietary salt intake and, as a result, did not reduce IDWG [166]. Telini et al. showed that restriction to 2-g sodium/day did not reduce IDWG [167]. Kayikcioglu et al. studied patients from two dialysis units, one dialysis unit was practicing an antihypertensive salt restriction–based strategy and the other dialysis unit practicing an antihypertensive drug-based strategy [168]. The patients who were in the salt restriction–based strategy did have significantly lower IDWG. In another study, nutritional counseling was conducted over 48 months and resulted in decreased salt and water intake, from 13.3 ± 2.7 to 11.8 ± 2.4-g sodium chloride/day and 2528 ± 455 to 2332 ± 410 g water/day [169]. Another important reason to provide dietary counseling to MHD patients on water and mineral intake is to reduce the risk that the patient's intake may deviate even further from an optimal diet.

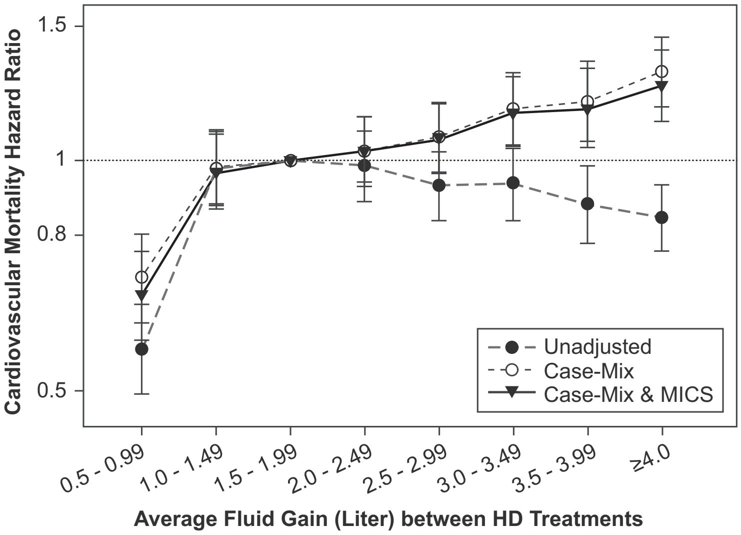

FIGURE 31.4 Association of fluid gain between two consecutive hemodialysis treatment sessions and 2-year cardiovascular mortality in 34,107 MHD patients. *MHD*, Maintenance hemodialysis. *Source: Adapted from Kalantar-Zadeh K, Regidor DL, Kovesdy CP, et al. Fluid retention is associated with cardiovascular mortality in patients undergoing long-term hemodialysis. Circulation 2009;119(5):671–9.*

Studies evaluating the relationship between interdialytic weight gain, hypertension, and mortality

The 2-year mortality was examined in 34,107 MHD patients in the United States [170]. The 3-month average IDWG was divided into eight categories of 0.5-kg increments: up to, greater than, or equal to 4.0-kg weight gain. Of these patients, 86% gained >1.5 kg between two dialysis sessions. Once multivariate adjustment was made for demographics and markers of the malnutrition–inflammation complex, higher weight gain increments (>0.5 kg) were associated with increased risk of all-cause and cardiovascular death (Fig. 31.4). These findings suggest that it is prudent to limit fluid gain between two subsequent HD sessions, as it is linked to higher risk of all-cause and cardiovascular death.

A number of smaller studies have shown that high IDWG contributes to hypertension, but some studies have not shown that relationship or found this relationship only in “volume-responsive” patients [171–173]. Hypertension in dialysis patients can be purely volume related, can be due to a combination of volume and hormone related (e.g., catecholamines, renin, angiotensin, and aldosterone), or can be purely hormone related. The association between the expansion in total body water or extracellular volume and hypertension is thought to be due to the associated increase in plasma volume and possibly vascular wall sodium.

In a large study of MHD patients, those with low IDWG were at higher risk of dying and also those with a very high IDWG had a modest increase in risk of death [174]. The patients with a low IDWG who had an increased mortality were probably patients who had increased comorbidity with PEW and poor oral intake. PEW, by itself, is a powerful predictor of poor outcome in MHD patients (see earlier). Even though there are some studies, usually involving inadequate number of patients, which show no relationship between IDWG and hypertension or mortality, the preponderance of evidence strongly indicates that it is important to keep IDWG to as low as tolerated by sodium and water restriction.

The sodium concentration in hemodialysate is another factor that has been examined for its relationship to IDWG. The Dialysis Outcome and Practice Pattern (DOPPS) study reported a decline in IDWG in the last decades in the United States and Europe [175]. This was in part explained by reduction in sodium in the hemodialysate. Studies are currently examining clinical outcomes with different dialysate sodium concentrations. Many dialysis centers use a sodium concentration of around 135–138 in the dialysate. The benefit of a reduction in IDWG with a lower dialysate sodium concentration has to be balanced against the risks of such adverse effects as hypotension [176].

Water intake

The majority of MHD patients are oliguric or anuric, and, therefore, water intake should be limited to 750–1500 mL/day, including the water consumed with food, unless the patient has urine output above the oliguric range. Too much water intake between dialysis treatments is one of the main reasons for excessive IDWG. Thirst, which is deranged, and xerostomia have been reported to lead to large IDWGs in dialysis patients [177].

Potassium

Before and after MHD is initiated, patients should receive detailed counseling on avoiding high potassium–containing foods. They must be informed about foods which have high-potassium content. Severe hyperkalemia (serum potassium of 7.0 mmol/L of greater) can precipitate fatal cardiac arrhythmias. In MHD patients a diet providing no >70 mmol/day (roughly 2.8 g/day) should be prescribed [178]. This restricted diet is tolerated by most but not all MHD patients. Education regarding diets that are low in potassium (i.e., ≤70 mEq/day) ideally should be conducted during the months and weeks leading up to inauguration of dialysis.

Epidemiological studies indicate that serum potassium >5.3 mEq/L is associated with increased mortality in MHD patients [179]. The dietary intake of potassium (estimated using the Block Food frequency Questionnaire) as a predictor of mortality was studied in 224 MHD patients [180]. Mortality was examined over a 5-year period, from 2001 to 2006. MHD patients with higher potassium intakes had greater dietary energy, phosphorous, and protein intake and had higher predialysis serum potassium and phosphorous [180]. Greater potassium intake was associated with significantly increased death risk in unadjusted models and after incremental adjustments for case-mix and such nutritional factors as the 3-month averaged predialysis serum creatinine, potassium, and phosphorous levels, Basic Metabolic Panel (BMP), nPNA, dietary energy, protein, and phosphorus intake, and also serum levels of inflammatory markers.

In the past, very low-potassium dialysate, containing 0–1.0 mmol K/L, was used in outpatient and incenter HD units, especially in the United States. However, there has been increasing awareness of the risks of sudden cardiac death associated with postdialysis hypokalemia. Due to this risk of postdialysis hypokalemia in MHD patients who were treated with very low-potassium dialysate, these dialysate solution has largely been abandoned in outpatient HD units. Karnik et al. reviewed records of 400 cardiac arrests over a 9-month period in a nationally representative cohort of 77,000 MHD patients dialyzed at outpatient HD units in North America [181]. They reported that cardiac arrests were nearly twice as likely to occur in patients who had been dialyzed with dialysate containing 0–1.0 mEq/L potassium on the day of the cardiac arrest (17.1% vs 8.8%). Since many large cohort studies have identified an increased risk of sudden cardiac death associated with very low-potassium dialysate (<2 mEq/L), most dialysis units, at least in the United States, avoid very low-potassium dialysate and employ longer hours (4 or more hours) per dialysis session to control serum potassium, if necessary [182]. It is also important to recognize the potential hazards of higher potassium (≥3 mEq K/L) dialysate concentrations. The association of mortality rates with dialysate potassium and predialysis serum potassium concentrations was examined in a cohort of over 81,000 MHD patients [179]. The greatest mortality was observed in patients who underwent MHD with dialysate potassium concentrations above 3 mEq/L or who had predialysis serum potassium levels of 5 mEq/L or higher. A study of Canadian MHD patients showed increased death rates when the dialysate potassium was 3 mEq/L or greater [183]. A similar finding of increased mortality with dialysate potassium ≥3 mEq/L was reported in the DOPPS cohort [184]. The safety of using graded dialysate potassium concentrations has not been examined in large-scale studies. It would seem prudent to use very low-potassium dialysate (<2 mEq/L) only during the first hour of HD in patients with hyperkalemia. This strategy needs to be examined in clinical trials.

A standard HD session removes 70–100 mEq of potassium (210–300 mEq/week) for patients who receive HD three times weekly. HD removes potassium from the extracellular compartment, which has only 2% of the total body potassium, whereas 98% of body potassium is in the intracellular compartment. The majority of potassium removed (almost 85%) during HD occurs through diffusion and is dependent on the dialysate–blood potassium gradient. Substantial losses of potassium occur through fecal excretion, especially in people with chronic kidney failure in whom fecal potassium excretion, roughly 17 mEq/day, is greater than normal [185]. It has been suggested that it is important to avoid constipation in chronic dialysis patients to prevent potassium accumulation and hyperkalemia.

New medications to lower serum potassium levels in maintenance hemodialysis patients

In patients who continue to have predialysis serum potassium >5.3 mEq/L despite strict dietary counseling and other dietary interventions, medications to lower serum potassium should be considered. First, recirculation of blood at the vascular access should be checked as a cause of persistent hyperkalemia before medications to lower potassium are prescribed.

Sodium zirconium cyclosilicate and patiromer are effective cation exchangers that exchange such cations as sodium and calcium for potassium in the gastrointestinal tract. When dietary counseling and dietary restriction are not effective, and MHD patients continue to develop hyperkalemia, these newer medications can be used. The binding affinity of these newer medications for potassium is high, and they are much more effective than sodium polystyrene. There is a risk of increased sodium absorption with zirconium. These medications should be avoided in patients who are postoperative from abdominal surgery, who take opiates, or who have poor gastrointestinal mobility from other causes. Limiting dietary intake of potassium remains the cornerstone of preventing and treating hyperkalemia.

Magnesium

A typical 24-hour diet contains approximately 360-mg magnesium of which there is net absorption of about 50% in the gastrointestinal tract. Normal kidneys excrete roughly 100-mg magnesium/day [186]. The normal plasma concentration of magnesium is 0.65−1.0 mmol/L (1.3−2.0 mEq/L or 1.6−2.4 mg/dL). Only 1% of total body magnesium is found in the extracellular compartment.

Hypomagnesemia can cause prolonged QT intervals and increase the risk of ventricular arrhythmias [187−189]. This risk is even more elevated if hypokalemia and hypomagnesemia are present together. Dialysis prescription for MHD patients, therefore, should be designed to avoid hypomagnesemia. Magnesium disorder occurs in dialysis patients more frequently is realized and, therefore, is not as commonly considered as it should be [190,191]. Mild hypermagnesemia is frequently present in MHD patients, but severe hypermagnesemia is rare. Hypermagnesemia, however, is more common if magnesium-containing antacids or laxatives, such as Maalox, Gelusil, milk of magnesia, or cascara sagrada, are consumed in large amounts or on a routine basis [186]. MHD patients are reported to have increased magnesium content in bone and soft tissues [192−194]. Patients with advanced CKD who are not on dialysis have a dietary magnesium requirement of about 2−4 mg/kg/day, which is about 200 mg/day [195]. MHD patients usually maintain normal or slightly elevated predialysis serum magnesium levels when their hemodialysate contains 1.0 mEq/L of magnesium.

Serum magnesium is approximately 25% protein bound and 5%−16% of serum magnesium is complexed with such anions as bicarbonate, phosphate, and citrate. Serum magnesium, therefore, is not freely cleared by the HD membrane [196]. The amount of magnesium cleared is dependent on the concentration of magnesium in the dialysate; therefore dialysate prescription is important. If the serum magnesium is in the normal range and the dialysate magnesium is 0.75 mmol/L, about 565 mg of magnesium will be cleared during a 4-hour standard HD session. If the serum magnesium is in the normal range and the dialysate concentration is 0.25 mmol/L, about 3100 mg of magnesium will be cleared. Alhosaini et al. reported that hypomagnesemia occurs 33% of the time at hemodialysate magnesium concentrations of 0.25 mmol/L (0.5 mEq/L) but occurs only 5% of the time in patients with hemodialysate magnesium of 0.5 mmol/L (1.0 mEq/L) [196].

Calcium

The Recommended Daily Allowance for calcium in normal nonpregnant, nonlactating adults is 1000−1200 mg/day. The daily calcium requirement is estimated to be 800−1000 mg/day in healthy adults as proposed by Institute of Medicine. In adults with CKD 3 and 4 who are not receiving active vitamin D analogs, daily calcium of 800−1000 mg/day is considered adequate to maintain calcium balance [14]. In advanced CKD and MHD patients, deficiency of various vitamin D compounds (e.g., 25-hydroxycholecalciferol and 1,25-dihydroxycholecalciferol) and resistance to the actions of vitamin D can increase the dietary calcium requirements. MHD patients are recommended to consume about 800−1000 mg of calcium/day. Phosphorus-rich foods are often rich in calcium, and restriction of high phosphate content foods will also reduce calcium intake. On the other the hand, it is not uncommon for MHD patients to take calcium-containing phosphate binders, and this can lead to calcium intakes of 1.0−1.5 g/day or greater. Daily calcium intake can exceed 3.0 g/day from a combination of calcium-containing phosphate binders and foods high in calcium content. A high calcium intake increases intestinal absorption of calcium, and this poses a risk for soft tissue calcium deposition. To control soft tissue calcification, including vascular calcification, the dialysate calcium is often prescribed at 1.25 or 1.5 mmol/L (5.0−6.0 mg/dL) in patients who take calcium-containing phosphate binders. Since much of serum calcium is protein bound or complexed to other compounds, in a patient with normal serum calcium concentrations, this level of ionized calcium in dialysate should lead to no calcium exchange or possibly a small transfer of dialysate calcium into the patient.

Goodman et al. were one of the first to show extensive coronary artery calcification in young adults with ESRD [197]. Several reports have raised concerns about the contribution of oral calcium intake to the development of coronary calcification and atherosclerotic plaques in MHD patients [198]. Calcium load and hyperphosphatemia accelerate vascular calcification [199−201]. A number of studies have shown that the risk of coronary artery calcification and vascular calcification is significantly reduced when noncalcium-containing phosphate binders, as compared to calcium-containing ones, are used [202,203].

Sevelamer hydrochloride is a popular intestinal phosphate binder that does not contain calcium. However, sevelamer hydrochloride may contribute to metabolic acidosis. In a randomized clinical trial of 129 incident MHD patients, calcium acetate was compared to sevelamer hydrochloride [204]. Coronary artery calcification was greater in the patients who used the calcium-containing phosphate binder [204].

These reports led to a consensus that calcium-containing phosphate binders should be avoided if possible. In the Dialysis Clinical Outcomes Revisited analysis, which compared calcium acetate to sevelamer hydrochloride, there was lower incidence of cardiovascular death and hospitalization in the calcium-binder group [205]. However, it is important to keep in mind that the sevelamer resin also binds and lowers serum cholesterol. In patients in whom calcium-containing phosphate binders are required, it is best to keep the calcium intake from foods <800 mg/day.

In large epidemiological studies of MHD patients, both high (>10.5 mg/dL) and low serum calcium levels (<8.0 mg/dL) are associated with an increased mortality risk [206]. Patients who receive both calcium salts and 1,25-dihydroxycholecalciferol (1,25-dihydroxyvitamin D) should be monitored for hypercalcemia. The risk of calciphylaxis, metastatic calcification, pruritus, and hypertension increases significantly in MHD patients when the serum calcium-phosphorous product exceeds 70. Therefore it is considered important to maintain the serum calcium–phosphorus product <60 [207,208].

Phosphorus (target range, phosphate binders, organic vs inorganic phosphorus)

Although randomized controlled trials are necessary to precisely define the optimum target level for serum phosphorus in MHD patients, a target range for serum phosphorous of 3.5–5.5 mg/dL seems reasonable [209]. Serum phosphorous levels >5.5 are associated with increased mortality [209–212].

Dietary phosphorous restriction is the cornerstone of the management of hyperphosphatemia in chronic dialysis patients. It is noteworthy that there are no randomized prospective studies that show reduction of serum phosphorous with medications (e.g., phosphate binders) reduces mortality in chronic dialysis patients [213], although such studies would be difficult to conduct today. Observational studies do support improved survival with phosphate binders [214,215].

The 2015–16 NHANES indicates that in American adults aged 20 and older, the average daily phosphorus intake from foods is 1189 mg for women and 1596 mg for men [216]. This is most likely a substantial underestimate of the actual phosphorus intake, because it does not include much of the daily phosphorus intake from food additives. Roughly 60% of ingested phosphorus is absorbed via the gastrointestinal tract. Organic plant–based phosphorus is absorbed to a somewhat lesser extent than inorganic phosphorus [217].

Depending on the predialysis serum phosphorus concentration and the dialysis dose delivered, approximately 250 mg of phosphorus is removed with each HD session [218]. Therefore HD alone is not a very efficient method to remove the increased phosphorus burden and elevated serum phosphorus commonly seen in MHD patients, and dietary phosphorus restriction is the key to serum phosphorus control. It is recommended that MHD patients consume about 10–17 mg/kg/day of phosphorous [14,195,219]. The phosphorous content of the diet is directly related to the quantity of protein, dairy products, and certain cola drinks in the diet [195,219]. Hypophosphatemia in MHD patients, which often indicates a poor appetite and a low-protein intake, as well as hyperphosphatemia, is associated with poor outcomes in MHD patients [220].

Very low–phosphorus diets (e.g., <800 mg/day) are often less palatable, and, therefore, patients may find it very difficult to follow severely restricted phosphorus diets. Moreover, since the protein and phosphorus content of the diet are usually correlated, it is usually difficult to substantially reduce phosphorus intake without decreasing the protein intake. Indeed, a typical method that dietary counselors may use to decrease dietary phosphorus intake is to reduce the protein intake as well. In a large epidemiological study, Shinaberger et al. found that MHD patients had a rise in protein intake (measured by the nPNA over 6 months) and a low predialysis serum phosphorous level had greater survival than the MHD patients who displayed a rise in both protein intake and serum phosphorus levels [84]. The worst survival was in those MHD patients who had a low-protein intake and low serum phosphorus levels [84]. These data underscore the importance of not inducing protein wasting during the process of implementing dietary phosphorus restriction.

Because severe dietary phosphorus restriction is usually impractical and the amount of phosphorus removed with usual HD, ≤4 hours thrice weekly, is insufficient to maintain normal predialysis serum phosphorus, phosphate binders that bind phosphorus in the intestinal tract are usually required. Phosphate binders are used to augment dietary phosphorus restriction to attain desirable serum phosphorus levels in MHD patients. The binders usually do not bind sufficient amounts of phosphorus to replace the need for low-phosphorus diets.

Aluminum-containing binders (aluminum hydroxide, aluminum carbonate) were among the earliest phosphate binders. These binders led to the serious side effects of low turnover bone disease, refractory anemia, and dementia. Calcium-containing phosphate binders were a significant improvement over aluminum-containing binders. Calcium carbonate contains 40% calcium by weight. Calcium acetate contains 25% calcium, and calcium citrate, 21% calcium. The major drawback of calcium-based binders is that they increase intestinal calcium absorption that is associated with enhanced calcium accumulation in soft tissue, including vascular calcification. Calcium-free phosphate binders, such as sevelamer hydrochloride, offered the advantage that it is polymeric amine and does not provide a calcium load; in addition, it binds lipids which results in lowering of serum cholesterol.

Aluminum-containing phosphate binders have superior phosphate-binding potency compared to most of the calcium-containing and calcium-free phosphate binders and, therefore, can be combined for short periods of time with other noncalcium binders for patients with very high serum phosphorus levels (e.g., serum phosphorus >8.0 mg/dL) or those with a serum calcium−phosphorus product of about 70 or greater. Calcium citrate should not be combined with aluminum-based phosphate binders because citrate increases intestinal aluminum absorption. Calcium acetate is a more effective phosphate binder on a weight-to-weight comparison, presumably because it is more effective at a broader range of pH and may be associated with less hypercalcemia. Some studies, however, indicate that the incidence of hypercalcemia is similar with both calcium acetate and calcium carbonate, and gastrointestinal symptoms such as nausea, bloating, and constipation are more common with calcium acetate [221,222]. Large doses of calcium-based binders are associated with higher risk of coronary artery calcification and have also been implicated as a cause of adynamic bone disease [197,223,224].

Preliminary studies indicate that sevelamer hydrochloride is associated with a lower incidence of both hypercalcemia and coronary artery calcification, possibly because of the cholesterol-binding properties of sevelamer [204]. The hydrochloride in sevelamer hydrochloride may lead to hyperchloremic acidosis, especially at higher doses (e.g., 4−7 g three times daily) [225]. Sevelamer carbonate, which does not contain the hydrochloride, does not cause metabolic acidosis [225].

Lanthanum carbonate and trivalent iron-containing compounds are other noncalcium-containing phosphate binders that are approximately as potent as the calcium-containing binders [226,227]. Unlike sevelamer hydrochloride, lanthanum does not cause metabolic acidosis. Individuals who take lanthanum carbonate develop small increases in tissue lanthanum levels; this has not resulted in any recognizable adverse side effects. Kendrick et al. reported results of 530 MHD patients who transferred from noniron-based phosphate binders to sucroferric oxyhydroxide. This resulted in a twofold higher likelihood of controlling serum phosphate in the target range and also was associated with a reduction in the daily pill burden.

There are currently no randomized controlled trials that conclusively establish the ideal predialysis or postdialysis serum phosphorus levels for MHD patients. Current recommendations, therefore, are based on observational studies and virtually exclusively focus on the predialysis serum phosphorus. Kalantar-Zadeh et al. examined the relationship between predialysis serum phosphorus levels and mortality in 58,000 MHD patients [228]. The risk of death was significantly higher with predialysis serum phosphorus levels equal to or greater than 6.0 mg/dL as compared to serum phosphorus levels of 5.0−5.99 mg/dL. The DOPPS data compared the hazard ratios for cardiovascular death in MHD patients with serum phosphorus levels of 5.0−5.99, 6.00−6.99, and ≥7.0 mg/dL. The hazard ratios for cardiovascular mortality were 1.25, 1.61, and 1.81, with serum phosphorus of 5.0−5.99, 6.00−6.99, and ≥7.0 mg/dL, respectively [229].

Vitamins

The recommended dietary intake of vitamins for MHD patients is shown in Table 31.3.

Causes of vitamin deficiencies in maintenance hemodialysis patients

The causes for vitamin deficiencies include (1) reduced food intake due to anorexia or comorbid conditions (e.g., sepsis, dementia, disseminated cancer, and emotional depression). (2) Prescription of low-phosphorous, low-potassium diets that restrict intake of foods that are higher in vitamin content, for example, fruits, vegetables, and fortified dairy products. (3) Dialysate losses of water-soluble vitamins. (4) Altered metabolism of certain vitamins, as is the case for pyridoxine (vitamin B6) and possibly folate. (5) Impaired synthesis, for example, impaired conversion in the failing kidney of 25-hydroxyvitamin D to 1,25-dihydroxyvitamin D. (6) Resistance to the actions of vitamins due to kidney failure (vitamin B6, vitamin D, and possibly folate). (7) Medicines that interfere with the actions or metabolism of vitamins. (8) Possibly decreased intestinal absorption of vitamins (decreased absorption of riboflavin, folate, and vitamin D); this has been described in rats with chronic renal insufficiency. Some medications taken by MHD patients may also interfere with intestinal absorption of vitamins. (9) Finally, some MHD patients are so impoverished that they are unable to purchase foods containing sufficient amounts of all vitamins.

Water-soluble vitamins (vitamins B1, B2, B3, B5, B6, B12, and C)

In the absence of vitamin supplements, MHD patients are at risk of developing deficiencies of water-soluble vitamins [230−234]. Patients who receive dialysis with high-flux dialyzers may also have a greater need for vitamin supplements, because these patients have higher losses of a number of water-soluble vitamins into dialysate [235]. Consequently, some investigators have recommended that MHD patients should routinely take folic acid and vitamin B supplements.

This is a controversial subject for which no clear consensus is available. Some studies report that MHD patients do not develop signs of vitamin deficiencies when followed for about 1 year without taking vitamin supplementation [236,237]. However, in some of these studies, it was not uncommon to find that mean blood measurements for some of the water-soluble vitamins decreased to near the borderline for low values. These findings make it very likely that the blood levels for some vitamins fell below the normal range in some patients.

It is important to note that many studies that suggest vitamin supplementation is needed were conducted in the 1960s and early 1970s when there was a much higher incidence of PEW in MHD patients [236]. However, some recent reports show that many MHD patients consume some vitamins in lower quantities than the recommended dietary allowances [238]. The foregoing data indicate that there is a small but persistent prevalence of deficiency for some water-soluble vitamins in MHD patients. At the present time, it is difficult to identify which MHD patients will develop vitamin deficiencies if they do not take vitamin supplements. The clinical condition of an MHD patient who is eating well may also change abruptly if the patient becomes ill, and the patient's vitamin intake from foods may fall. Moreover, if the patient receives medical attention for an illness, he/she may receive medicines that interfere with vitamin nutrition. Hence, such a person may suddenly develop a need for vitamin supplements.

Since water-soluble vitamins appear to be safe and not very expensive and it is often not possible to predict when MHD patients need vitamin supplements, we believe a strong case can be made that multivitamin supplements should be offered to virtually all MHD patients. A case in point is the study by Kalantar-Zadeh et al. of 30 normal individuals who were compared with 30 MHD patients that were matched for age, gender and race [239]. Their food intake was assessed by FFQs. The findings indicated that MHD patients consumed statistically significantly lower amounts of vitamin C, potassium, dietary fiber, and lower amounts of some carotenoids, including cryptoxanthin and lycopene. This lower intake of vitamin C, fiber, and carotenoids may be atherogenic. The lower vitamin intake in these MHD patients may be the result of the restriction of their dietary phosphorous and potassium intake. Dietary restrictions in MHD patients may lead to reduced intake of fruit, vegetables, and milk, which may leave meat, fats starchy food (breads, crackers), and sugars as the main sources of their calories.

Oral vitamin C supplements may promote intestinal iron absorption and reduce the incidence of iron deficiency in MHD patients (see Chapter 38: Nutrition and Anemia in Chronic Kidney Disease) [240−243]. Folic acid supplements may reduce the elevated serum homocysteine levels that occur in ESKD (End Stage Kidney Disease) to normal or near-normal. Maximum homocysteine-lowering effects with folic acid occur at doses of 5−10 mg/day [244,245]. However, studies that examined the potential effects of folic acid supplementation on cardiovascular deaths or all-cause mortality have not shown significant benefits. Advanced CKD and ESKD patients in the HOST study were randomized to receive pharmacological doses of folic acid, pyridoxine HCl (vitamin B6), and vitamin B12 [246]. The patients receiving this vitamin mix, in comparison to those receiving placebo, did not show improvement in total mortality or cardiovascular mortality [246].

In MHD patients, serum or erythrocyte levels of thiamin (vitamin B1), riboflavin (vitamin B2), pantothenic acid, and biotin are usually normal. Case reports of Wernicke's encephalopathy in MHD and CPD patients due to thiamin deficiency have been published [247,248]. Niacin (vitamin B3) levels are usually normal, although Lasker et al. reported low niacin levels in MHD patients [236,237,249−251]. Pyridoxine (vitamin B6) is removed by HD and its metabolism appears to be altered in advanced CKD and ESKD patients [252,253]. These two factors result in an increased daily requirement for vitamin B6. A supplement of pyridoxine HCl, 5 mg/day, for nondialyzed advanced CKD and CPD patients and 10 mg/day for MHD patients appears to satisfy the daily requirement for vitamin B6 [253]. Vitamin C is recommended only at the daily allowance of 70 mg/day because of the risk of oxalate formation increases progressively as vitamin C intake rises (refer to Chapter 26: Vitamin Metabolism and Requirements in Chronic Kidney Disease and Kidney Failure).

Fat-soluble vitamins (vitamins D, K, A, and E)

Fat-soluble vitamins are not removed by HD. Nonetheless, there is often a need for supplements of some fat-soluble vitamins. Deficiencies of 25 CKD and MHD patients who do not take supplements of these vitamins (please also see Chapter 23: Calcium, Phosphate, PTH, Vitamin D, and FGF-23 in CKD-Mineral and Bone Disorder, Chapter 25: Vitamin D in Kidney Disease).

Vitamin K

Two classes of vitamin K compounds (phylloquinone that is vitamin K_1 and menaquinones that is vitamin K_2) are primarily responsible for vitamin K activity [254]. Since MHD patients do not generally have evidence of vitamin K deficiency unless they have been eating poorly or were on antibiotics that suppress intestinal bacterial vitamin K synthesis, supplemental vitamin K is not recommended for routine use. Vitamin K supplementation is required in patients who have suppressed intestinal absorption of vitamin K by antibiotics while they are not receiving vitamin K parenterally. KDOQI guidelines state that "it is reasonable that patients receiving anticoagulant medicines known to inhibit vitamin K activity (e.g.: warfarin compounds) do not receive vitamin k supplements" [14]. Some observational studies have indicated that in patients with advanced CKD (stages 3–5) or MHD patients serum vitamin K_1 and K_2 were low [255,256]. It has been reported that vitamin K status should be evaluated by using serum dephosphorylated-uncarboxylated Matrix Gla Protein (MGP) (dp-ucMGP) to determine whether CKD 3–5D patients should receive supplemental vitamin K. Vitamin K enables normal calcification process to occur in bone and soft tissue and, therefore, prevents soft tissue and vascular calcification. However, at this time, there is insufficient evidence to recommend providing supplemental vitamin K to correct high levels of serum dp-ucMGP to reduce the risk of arterial calcification in MHD patients. Westenfeld et al. were able to reduce dp-ucMGP levels with vitamin K2 supplements (45,135, or 360 μg/d) in a dose-dependent fashion [256]. Several reports have described ectopic tissue calcification in MHD patients who have high levels of serum dp-ucMGP levels [257]. In one study in MHD patients, treatment with pharmacological dose of vitamin K2 (45 mg/day orally) for 1 year was found to prevent bone loss, where bone disease was characterized by bone turnover [258]. An inverse relationship between the frequency of bone fractures and plasma phylloquinone levels was reported in MHD patients. In this study, serum Parathyroid Hormone (PTH) was high (> 300 ng/L) in patients with low plasma phylloquinone (vitamin K1) concentrations who also had an abnormally high apolipoprotein E phenotype [259].

Vitamin A

MHD patients, including those undergoing HD for many years, have increased serum vitamin A levels [260–262]. Vitamin A–retinol-binding protein (RBP) transthyretin complex is large in size and, therefore, is not lost into hemodialysate [263]. The HD process, itself, for this reason does not decrease serum vitamin A levels, and many CKD patients also have increased vitamin A levels and, as with MHD patients, do not show evidence of vitamin A toxicity [263]. RBP, which is the carrier protein for vitamin A, is degraded in the kidney. In renal failure, serum RBP and, hence, serum vitamin A are elevated, presumably because of reduced degradation of RBP by the failed kidney. However, even an extensively diseased kidney may continue to degrade some RBP. This may explain why MHD patients who had bilateral nephrectomy appear to have higher serum retinol levels as compared to other MHD patients [264,265]. β-carotene, ubiquinol, and lycopene are reported to be lower in MHD patients [266]. Werb et al. showed a positive correlation between plasma vitamin A concentrations and both serum total cholesterol and triglyceride levels [267]. The hematocrit is reported to correlate with plasma vitamin A/RBP ratio in MHD patients which may be suggestive that vitamin A levels promote erythropoiesis [268].

Patients with advanced CKD or ESRD are prone to develop vitamin A toxicity even relatively small doses of vitamin A. MHD patients ingesting the modest doses of 7500–15,000 units/day of vitamin A [about 2250–4500 retinol activity equivalents (μg RAE) of vitamin A] have been described with hypercalcemia and elevated alkaline phosphatase levels [269]. By comparison the recommended dietary allowance for vitamin A is 900-μg RAE for men and 700-μg RAE/day for nonpregnant, nonlactating women [270]. For this reason, it is recommended that the daily vitamin A intake from food and supplements combined for MHD patients should not exceed the recommended dietary allowances of 900- and 700-μg RAE/day [270].

Vitamin E (alpha-tocopherol)

HD removes little vitamin E and does not materially change serum vitamin E levels. Serum vitamin E has been reported to be low, elevated, or even unchanged in MHD patients [271–273]. Chazot et al. found that long-term MHD patients who had received HD for an average of 274 ± 35 (SD) months had serum vitamin E levels that were increased and not different from

10 age- and gender-matched patients who had received MHD for 51 ± 29 months [274]. Data regarding red cell tocopherol concentrations in MHD patients are contradictory [271,275]. These findings in some MHD patients may reflect increased consumption of tocopherol, possibly due to oxidative stress or to a defect in the HDL-mediated transfer of tocopherol from plasma to RBC membranes. Cohen et al. showed that RBC tocopherol concentrations were low in MHD patients who had sustained hemolysis due to high dialysate chloramine concentrations. The Red Blood Cell (RBC) tocopherol levels increased after chloramine was removed from the hemodialysate [276].

A number of studies, including a metaanalysis, have examined the effect on MHD patients using vitamin E−coated dialyzer membranes, but results were inconclusive [277−279]. The SPACE study was a double-blind, prospective clinical trial of 196 MHD patients who were randomized to receive supplements of oral vitamin E (800 IU/day) for a median of 519 days or placebo [280]. The MHD patients assigned to vitamin E treatment displayed a reduction in adverse cardiovascular events ($RR = 0.46$) and myocardial infarction ($RR = 0.30$) [280]. The relative risk in the SPACE study for ischemic stroke, peripheral vascular disease was not significantly different between the groups. Smaller studies on vitamin E supplementation did not confirm these reductions in morbidity or mortality. The HOPE study did not show the clinical benefits in patients with mild-to-moderate CKD (serum creatinine equal to or greater than 1.4−2.3 mg/dL) that were observed in the SPACE study [281]. The participants in the HOPE study who received vitamin E were given 400 IU daily for a median of 4.5 years. In the HOPE study, there was no difference between the placebo- and vitamin E−treated groups in total mortality. There was also no difference in the relative risk of Myocardial Infarction (MI), death from cardiovascular causes, stroke, heart failure, hospitalizations due to heart failure between the two groups. Moreover, a follow-up analysis of the HOPE study and its extension (HOPE-TOO) indicated an increased risk of heart failure in those patients who continued to receive long term the vitamin E supplements [282]. Since advanced CKD and MHD patients are at increased risk for oxidative stress and adverse cardiovascular events and because a vitamin E intake of 15 IU/day seems to be fairly safe, it is reasonable to prescribe a vitamin E supplement of about 15 IU/day to these patients.

Carnitine

Carnitine is synthesized by the liver and the kidneys and is also ingested in foods we consume. Carnitine facilitates the transfer of long-chain fatty acids (>10 carbon) into skeletal muscle mitochondria [283]. It is the free, unacylated carnitine that facilitates this transfer. Carnitine is necessary for muscle function as fatty acids are the major fuel source for muscle during both rest and mild-to-moderate exercise. Serum total carnitine levels are often normal in MHD patients, but free carnitine levels are usually below normal and acylcarnitine (fatty acid carnitine esters) levels are elevated [284]. Free carnitine levels in skeletal muscle are often, but not always, low in MHD patients [285,286].

Some but not all studies of L-carnitine supplementation in patients with renal failure reported increased blood hemoglobin levels, reduction in such intradialytic symptoms as hypotension and muscle cramps, and decreased hyperlipidemia [287,288]. L-Carnitine has also been reported to increase skeletal muscle exercise capacity, improve sense of well-being, and reduce postdialysis asthenia and malaise [289−291].

One randomized double-blind prospective clinical trial reported that L-carnitine decreased predialysis serum urea, creatinine, and phosphorous concentrations and increased mid-arm muscle circumference [290,291]. Interpretation of these data must be qualified because a number of outcome measures that showed improvement are imprecise or difficult to quantitate, not all randomized blinded studies showed benefits, and a number of the studies reporting benefits were not randomized, prospective, or blinded. With L-carnitine treatment, some clinical trials show improvement in serum lipid profiles but some clinical trials did not show benefit, and some studies reported an increase in serum triglyceride levels [292,293]. Due to these conflicting results, the therapeutic value of L-carnitine for MHD patients cannot be considered established. On the other hand, a number of blinded prospective studies did show benefits, and L-carnitine appears to be safe to be used in MHD patients [294,295].

While we await more definitive data, L-carnitine might be considered for use in the following clinical situations when all standard treatments have not resolved the problem:

1. anemia that is resistant to erythropoiesis-stimulating agents, iron, and vitamin therapy and with no evident cause;
2. intradialytic hypotension or muscle cramps;
3. impaired skeletal muscle exercise capacity;
4. postdialytic asthenia or malaise.

Before prescription of L-carnitine is given for the previous conditions, a thorough medical evaluation for other treatments should be conducted. The optimal dosage and route for therapy for L-carnitine are not defined at this time. The US Center for Medicare and Medicaid Services has recently approved coverage for use of L-carnitine for MHD patients if they have low plasma-free carnitine levels (<40 μmol/L) and either erythropoietin-resistant anemia or hypotension during HD. Continued coverage of L-carnitine treatment is not given unless improvement can be demonstrated. L-Carnitine can be given intravenously at a dose of 10–20 mg/kg given three times per week at the end of each dialysis session or it can be given orally at a dose of 5–10 mg/kg/day.

Management of protein-energy wasting in maintenance hemodialysis patients

A general approach to an maintenance hemodialysis patient with protein-energy wasting

Patients who show evidence of PEW or at high risk of developing PEW may be managed with the following steps to prevent or treat this condition:

1. Perform a thorough medical and social history, physical examination, psychological evaluation, and protein-energy (nutritional) assessment as indicated in Tables 31.1 and 31.2.
2. Identify the causes of the declining nutritional status. This assessment should include evaluating intake of dietary protein, energy, and other nutrients (e.g., using Urea Nitrogen Appearance (UNA) and dietary interviews and food dairies), examine for the presence of acute illnesses, exacerbation of established comorbid illnesses, nonspecific inflammation (e.g., an isolated increase in CRP), and acidemia. The causes for reduced food intake and acidemia should be investigated. Reduced intake of a healthy diet, for example, could be caused by anorexia which, in turn, may be due to inadequate dialysis dose or psychological depression. Other causes of reduce dietary intake are poverty, poor dentition, or inadequate social and family support. The patient's nutritional requirements should be evaluated.
3. Prompt therapy of any treatable comorbid condition (e.g., chronic infection, emotional depression with anorexia) that may contribute to PEW.
4. Counsel the patient and spouse or significant partners, and other members of the patient-family unit concerning the appropriate nutritional intake for the patient and strategies to attain it.
5. If the nutrient intake is inadequate in spite of appropriate dietary counseling, the following interventions may be employed:
    a. Provide frequent high-energy, high-protein foods, food supplements, or supplements of specific nutrients (e.g., multivitamins, calcium iron, and zinc). If dietary adherence is questionable, these foods and supplements at least can be provided in the HD unit on the HD day.
    b. Tube feeding.
    c. Intradialytic parenteral nutrition (IDPN) (see Chapter 45: Intradialytic Parenteral Nutrition, Intraperitoneal Nutrition, and Nutritional Hemodialysis).
    d. Daily total parenteral nutrition (TPN).

Oral nutritional supplements, tube feeding and intravenous nutrition for patients with inadequate food intake

Oral nutritional supplements

Nutritional status has been shown to improve when dietary counseling and oral nutritional supplements (ONS) are given to MHD patients who have PEW [296–298] (see Chapter 44: Oral and Enteral Supplements in Kidney Disease and Kidney Failure). A review of the evidence that nutritional support can improve protein-energy status, reduce PEW, and decrease the mortality risk in MHD patients has recently been published [299]. A minimum of 3 months trial of ONS is suggested in patients at increased risk for PEW or with PEW [14]. Studies have shown benefits from one can of a nutritional supplement given three times a week during HD session [300]. ONS, such as Ensure and Boost, are rather inexpensive and can be recommended for patients who do not have hyperkalemia or volume overload. For patients who have a history of hyperkalemia or volume overload, low-potassium, low-phosphorus supplements, such as Nepro, or Novasource Renal, can be recommended as they have 30%–35% less potassium and phosphorus content per mL and double the amount of calories and protein.

Tube feeding

It is important to recognize that long-term compliance to ONS by MHD patients is low, in part, because these patients are usually financially constrained, and, in many countries they must purchase the ONS. In the authors' experience, even when MHD patients are given ONS at no cost to themselves, only about 20%–40% of these patients will take them on a continuing basis for several or more months. MHD patients often tire of these supplements.

Patients who, despite dietetic counseling, will not ingest adequate nutrients, even with ONS, may be considered for tube feeding. Tube feeding may be more effective and less expensive [301,302]. It has been shown to be effective in pediatric patients receiving chronic dialysis. More studies are needed evaluate the effects of tube feeding on clinical outcomes, especially in adult CKD and chronic dialysis patients.

Intradialytic parenteral nutrition

IDPN is discussed in more detail in Chapter 45, Intradialytic Parenteral Nutrition, Intraperitoneal

TABLE 31.6 Intradialytic parenteral nutrition (IDPN) advantages and disadvantages in maintenance hemodialysis patients.

IDPN	
Advantages	**Disadvantages**
• Can give hyperosmolar, concentrated admixtures through the extracorporeal circuit during the HD session	• Since dialysis is usually three times a week, IDPN can be given only three times a day limiting this therapy to only 3 days a week
• Noncompliant patients and patients who have poor appetite can receive nutrition as IDPN is given during hemodialysis session	• Intravenous infusion of nutrients in a relatively short-time interval which may limit the efficient utilization of nutrients
• IDPN can overcome gastrointestinal function disorders in HD patients like gastroparesis	• It is more expensive than oral supplements • Nurses' workload is increased
• The exact dose of nutrients can easily be calculated and administrated	
• The amount of fluids delivered with nutrients can be removed simultaneously by the hemodialysis procedure	

HD, hemodialysis.

Nutrition, and Nutritional Hemodialysis. Although IDPN is insufficient to meet, by itself, the energy and protein needs of normal MHD patients or MHD patients with PEW, it can be considered as a nutritional supplement when an adequate trial of oral supplements and tube feeding (enteral nutrition) have not eradicated or improved protein-energy status or when PEW appears to be worsening [14]. When patients have barriers to ONS or tube feeding (e.g., patient resistance to ONS or tube feeding, loss of sense of taste, logistical problems), IDPN can be considered earlier in the treatment strategy. To provide adequate nutrition, IDPN must be given with some other source of nutrients, for example, some oral intake of foods or ONS or some amount of tube feeding.

IDPN offers both advantages and disadvantages (Table 31.6). It is convenient to give the intravenous solutions during HD which removes the issue of compliance, although about 30% of the amino acids provided by IDPN are lost into dialysate. It is also important to note that studies have shown significant losses of amino acids in a regular HD session in MHD patients who are not receiving IDPN [5,6,303]. Wolfson et al. found that 12.6 ± 3.6 SD g of amino acids were lost when MHD patients received an intravenous infusion of 39.5 g of amino acids during HD using inefficient hemodialyzers [5]. On the other hand, Ikizler found amino acid losses during high-flux HD of 8.0 ± 2.8 g when patients did not receive IDPN [6]. Thus the increase in amino acid, losses during HD with IDPN, as compared to HD in the fasting state, is quite modest.

Although IDPN is probably helpful in some patients, many case reports and studies which reported benefits with IDPN were not been well designed and did not have sufficient statistical power to offer firm conclusions.

IDPN solutions are prepared from base solution components. The base solutions for carbohydrates, amino acids and lipids can vary in concentration. Trace elements, vitamins, and minerals can be added to IDPN. The base solution from which a typical IDPN solution is prepared contains typically 40%−50% glucose, 10% amino acids and 10%−20% lipids.

Total parenteral nutrition

When MHD patients are unable to eat and cannot be nourished by tube feeding, usually because they have undergone surgery or developed acute catabolic illness, they frequently must be given TPN to satisfy their daily nutritional requirements. TPN often must be modified extensively, because MHD patients have limited tolerance for nitrogenous products, water, and many minerals, especially when they are acutely ill. The principles and techniques of nutritional support for MHD patients are similar to the methods used in acute kidney injury (AKI) as discussed in Chapter 35, Metabolic Management and Nutritional Support in Acute Kidney Injury. Nutritional support during the treatment of kidney failure patients with continuous renal replacement therapy is discussed in Chapter 46, Nutritional Management of Patients Treated With Continuous Renal Replacement Therapy.

Pharmacological agents to improve protein-energy status

Megestrol acetate

Megestrol acetate is a progestational agent that has been shown to improve appetite, food intake, and edema-free body weight in patients with carcinomatosis or AIDS [304−306]. However, in patients with

AIDS the increase in edema-free body weight was due to the accumulation of body fat rather than protein gain. There are currently no data in large-scale clinical trials that demonstrate that megestrol acetate improves appetite or protein-energy status in anorectic and protein-energy wasted MHD patients although small studies show trends toward some benefit [307–309].

Recombinant human growth hormone and insulin-like growth factor-I

Several small clinical trials have examined a possible beneficial role of GH or IGF-I in advanced CKD and MHD patients [310–314]. GH administration can reduce net protein catabolism and wasting, improve nutritional status, and decrease SUN levels in MHD patients. This benefit is largely or entirely mediated by an increase in IGF-I levels. However, significant long-term nutritional benefits of GH are not consistently observed, and the effects of GH and IGF-I on morbidity and mortality are not clear at this time [315–318]. Patients with advanced CKD exhibit resistance to both GH and IGF-I [310,319]. However, pharmacological doses of these agents still exert their effects on catabolism, growth, and hyperfiltration. Adverse effects of GH include hyperglycemia and, in large doses, acromegaly. Administration of GH to critically ill patients should be avoided, as it may increase mortality [320]. Additionally, in the doses currently used, IGF-I can cause hypoglycemia; when given intravenously, IGF-I may cause cardiac arrhythmias [313].

Zeigler et al. gave GH, 5–10 mg subcutaneously after each HD, to five MHD patients for 2 weeks [321]. They were prescribed a fixed protein and calorie diet. The serum urea decreased by 20%–25%. Schulman et al. treated seven malnourished MHD patients with IDPN for 12 weeks [322]. During the last 6 weeks, they also received GH with each dialysis. With GH treatment the PNA decreased from 0.81 ± 0.04- to 0.67 ± 0.03-g protein/kg/day, and there was an increase in serum albumin levels. Kopple et al. studied six MHD patients in a research ward for up to 35 days [323]. After a baseline period up to 14–21 days, the patients were administered 0.05-mg GH/kg body weight/day for 17 ± SEM 2 days. Two participants, patients 3 and 4, experienced an acute illness during the study that resulted in a reduction in their protein and energy intakes. With GH treatment, predialysis serum urea fell markedly in patients 1,2, 5, and 6 and to a much lesser degree in patients 3 and 4. Nitrogen balance was robustly positive in patients 1, 2, 5, and 6 but was less so in patients 3 and 4 [323]. The foregoing data indicate that GH induces an anabolic response in MHD patients with PEW [324].

Frequent hemodialysis, longer hemodialysis sessions, biocompatible dialyzer membranes

A number of modifications of standard HD therapy have been investigated to improve the clinical status of MHD patients. This modification includes longer duration and/or more frequent HD sessions, including both daily (quotidian) and nocturnal HD [325–328]. Longer HD sessions are usually conducted for about 6–8 hours per session, often with lower blood flow rates at 200–250 mL/min [329]. More frequent HD sessions are usually conducted 5 or 6 days a week with lower blood flow rates of about 200–300 mL/min and dialysate flows of approximately 200–300 mL/min [330]. Biocompatible HD membranes, which are commonly high-flux membranes, are commonly used [331]. It is thought that these modifications in the traditional basic HD techniques of longer or more frequent HD treatments or more biocompatible membranes may reduce the severity of uremic symptoms and inflammation. Daily HD and nocturnal HD also allow MHD patients to have a less restrictive protein, mineral, and water intake [332,333].

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CHAPTER

32

Nutritional management of chronic peritoneal dialysis patients

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Introduction

Peritoneal dialysis (PD) is based on the concept that the peritoneum may serve as a natural wearable inherent semipermeable membrane and dialyzer for removing solutes and water on a daily basis. A major advantage is that PD does not require blood access and that the gentle dialysis procedure results in steady, low metabolite levels, and steady control of fluid status without the rapid fluctuation in plasma solutes and fluid that occurs with hemodialysis (HD).

The dialysis solution is periodically instilled and drained from the peritoneal cavity through a PD catheter and is performed at home by the patient or by a caregiver after receiving careful training. The most common modalities of PD are continuous ambulatory PD (CAPD) and automated PD (APD). CAPD is performed manually with three to five exchanges per day. Each exchange has 1.5−3.0 L and the dwell time varies from 4 to 10 hours. The APD is performed by a cycler at night usually with 3−9 exchanges (cycles) over a period normally of 8−12 hours. Depending on the clinical needs of each patient, in addition to the APD, a manual exchange may be performed during daytime.

Different from the treatment with chronic HD, which is normally performed three times per week in a dialysis clinic, PD is usually performed at home every day. Because of its continuous nature, PD provides better metabolic control of mineral, fluid, and hydration status. On the other hand, since the dialysis fluid, in most cases, contains glucose as the osmotic agent, nutritional disadvantages may occur from the glucose absorption, depending on the clinical and nutritional condition of the patient. Indeed, it is estimated that 40%−60% of glucose in the dialysate is absorbed, which yields approximately 300−450 kcal/day depending on the dialysis modality, the glucose concentration of the dialysate, the dwell time of the dialysate in the peritoneal cavity, and the transport characteristics of the peritoneal membrane [1]. In addition to glucose absorption, the protein losses that occur during PD treatment, due to the size of the peritoneal membrane pores, confer another nutritional disadvantage leading to lower serum albumin concentrations [1]. Also of importance, a significant proportion of patients with end-stage renal disease (ESRD) are aged 65 years and older, and the mean age of the individuals undergoing dialysis has increased substantially over the years [2]. Therefore particularities related to aging also require special attention when treating the nutritional aspects of PD [3]. This chapter reviews briefly the nutritional aspects of PD and describes the nutritional needs and strategies to prevent and treat the main nutritional disturbances that occur in PD patients.

Main nutritional disturbances in patients undergoing peritoneal dialysis

The nutritional disturbances that are most prevalent in PD patients are protein-energy wasting (PEW), sarcopenia, and obesity with estimated prevalences as described in Table 32.1. A summary of other nutritional issues related to the modality of PD, as well as suggested nutritional interventions, are presented in Table 32.2.

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TABLE 32.1 Estimated prevalence of protein-energy wasting, sarcopenia, and obesity in peritoneal dialysis patients.

	Prevalence (%)	Study
Protein-energy wasting[a]	39–49	Carrero et al. [4]
	35.6	Vasselai et al. [5]
	22	Young et al. [6]
	19	Melo et al. [7]
Sarcopenia[b]	11	Abro et al. [8]
	10	Kamijo et al. [9]
	11.5	As'habi et al. [10]
Obesity[c]	15.6	Vasselai et al. [5]
	13	Fernandes et al. [11]
	36.5	Obi et al. [12]
	17.4	Prasad et al. [13]

[a] *Assessed by subjective global assessment or malnutrition inflammation score.*
[b] *Defined as low muscle mass and low muscle strength.*
[c] *Defined as body mass index ≥30 kg/m2.*

TABLE 32.2 Main nutritional disturbances in peritoneal dialysis and suggested nutritional interventions.

Nutritional disturbance	Nutritional intervention
1. Spontaneous body weight loss/malnutrition/sarcopenia	Consider counseling more frequent meals with small content of food per meal
	Eat meals in between the dwell exchanges when the peritoneal cavity is empty. Some patients complain of early satiety due to higher intraperitoneal pressure with fluid in peritoneal cavity
	Consider using energy and/or protein supplements (oral drinks or powders) to increase total energy and protein intake
	Evaluate dialysis adequacy and adjust the dialysis dose when needed
2. Protein loss in the dialysate/hypoalbuminemia	Evaluate if protein intake is matching the protein needs
	Add extra-sources of protein into meals (e.g., egg white, whey protein)
3. Early satiety	Avoid drinking liquids with meals
	Preferably, eat meals in between the dwell exchanges
4. Obesity	Reduce the intake of foods rich in fat and sugar
	Increase physical activity (under supervision)
	Replace some of the exchanges with glucose-based solutions with icodextrin- and/or amino acid–based solutions
5. Hypertriglyceridemia	Reduce the intake of foods rich in sugar
	Reduce the glucose concentration of the dialysate and replace some of the exchanges with glucose-based solutions with icodextrin- and/or amino acid–based solutions, if available
	Increase physical activity (supervision)
6. Hypercholesterolemia	Reduce the intake of foods rich in saturated fat and trans-fat
	Treatment with statins or other cholesterol lowering drugs
	Increase the intake of fiber (grains, vegetables, and fruits)
7. Intestinal constipation	Increase the intake of fiber (grains, vegetables, and fruits) and water
	Increase the use of vegetable oils (olive or linseed)
8. Hypokalemia	Increase the intake of grains, vegetables, fruits, and nuts
9. Hyperphosphatemia	Avoid the use of foods with a high-ratio phosphorus (mg)/protein (g) (e.g., dairy products, sardine, and liver)
	Combine the use of phosphate binders with the meals or snacks with food sources of phosphate
	Adjust the dose of phosphate binders according to the amount of phosphate in the meal
	Treat hyperparathyroidism

Protein-energy wasting, malnutrition, and sarcopenia

PEW was defined by an expert panel of the International Society of Renal Nutrition and Metabolism (ISRNM) as a "state of decreased body stores of protein and energy fuels (that is, body protein and fat masses)" [14]. PEW can be caused by a number of factors, including (1) insufficient food intake characterized by decreased intake of energy, protein, and other nutrients; (2) increased net protein catabolism and energy expenditure, due to low grade inflammation, acidemia, activation of

TABLE 32.3 Etiological factors of protein-energy wasting specific to peritoneal dialysis (PD).

Outcome	Specific PD etiological factors
Low appetite and decreased energy and nutrient intake	Glucose absorption from the dialysate
	High intraabdominal pressure
	Inflammation
Increased protein catabolism	Inflammatory factors
	Peritonitis
	Nonbiocompatible dialysate solutions
Loss of nutrients in the dialysate	Amino acids and peptides: 3 g/day
	Protein: 5−15 g/day
	Vitamins B and C

Note: PD patients lose into dialysate water-soluble vitamins plus to some extent also fat soluble vitamins that are protein bound (due to the 5−15 g/day of protein losses into dialysate).

the ubiquitin−proteasome pathway, intercurrent catabolic illnesses such as peritonitis, hyperparathyroidism, and others; (3) nutrient losses into the dialysate, which play an important role in PD patients, as there are losses of amino acids, peptides, protein, and water-soluble vitamins into the dialysate; and (4) resistance to anabolic hormones (e.g., insulin, growth hormone, insulin-like growth factor 1, and testosterone) [15]. More recently, ageing [16] and a nonhealthy gut microbiota have also been suggested as nontraditional etiological factors for PEW and inflammation in chronic kidney disease (CKD) [17] (please see Chapter 11: The Gut Microbiome and the Kidney, and Chapter 13: Causes and Treatment of Protein-Energy Wasting in Kidney Disease).

PD-specific factors involved in the etiology of PEW are depicted in Table 32.3. Decreased appetite, a common condition in PD patients, seems to be an important factor [6]. Of note, a study comparing hunger, fullness scores, and energy and protein intake between PD and healthy individuals indicated that patients undergoing PD showed significantly lower sensations of hunger before meals and a flatter sense of fullness profile during the day, indicating lower feelings of hunger throughout the day. These PD patients also displayed a lower energy and protein intake [18]. Altogether, these findings are suggestive that lower appetite can lead to malnutrition. Corroborating this hypothesis, Melo et al. [7] recently showed in a study of PD patients, comprising mostly APD patients, that those in the tertile with the lowest appetite score, as assessed by an appetite questionnaire, had significantly lower ratings in the 7-point subjective global assessment (SGA) score, handgrip strength, phase angle, lean body mass index (BMI), and fat mass index when compared to the tertile with the highest appetite.

The factors causing low appetite in PD patients are still under debate. Glucose absorption from the dialysate—an involuntary energy input—was shown to account for 15%−26% of total energy intake in a group of PD patients [19]. This involuntary input of glucose and energy is metabolically equivalent to a "fed state or postabsorptive state," and the normal physiological stimuli to enhance appetite, such as low serum glucose and insulin levels and high ghrelin levels, are attenuated [20]. Thus these processes most likely lead to low appetite and a reduced energy and nutrient intake, although in a cohort study the amount of glucose absorption from the PD fluid was not associated with lower energy or protein intake [21]. Another factor diminishing appetite in PD patients is the increase in intraabdominal pressure caused by the infusion of the dialysate in the peritoneal cavity. This can lead to abdominal discomfort and increase satiety, mainly in patients treated with CAPD who perform dialysate exchanges during the day [20]. Indeed, Hylander et al. [22] showed that patients undergoing CAPD had a tendency to be less hungry before lunch when there was dialysate solution in the abdomen as compared to when the abdominal cavity was empty of dialysate. Finally, increased serum levels of proinflammatory markers have been reported in PD patients with decreased appetite [23]. Proinflammatory cytokines are well-described anorectic agents, and these findings suggest that inflammation may be another cause of decreased appetite in PD patients. The pathways explaining this association are not clear, but the anorectic actions of inflammation most likely include both decreased motility of the gastrointestinal tract and an increase in serum leptin levels, an anorexic hormone [20]. We reported a significant direct association between serum leptin and C-reactive protein concentrations in PD patients [24]. Altogether, PD patients are prone to the development of protein wasting, which is characterized by a condition of decreased protein mass (i.e., skeletal muscle mass) that is not necessarily accompanied by decreased fat stores (i.e., body fat).

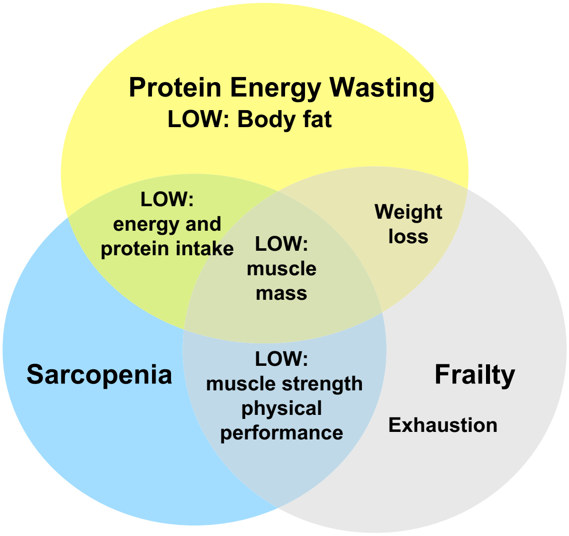
In this regard, it is also important to describe sarcopenia, understood as another nutritional disorder defined as the loss of muscle mass and muscle function (i.e., low muscle strength and/or physical performance) (see Chapter 12, Assessment and Risk Factors for Protein−Energy Wasting and Frailty in Chronic Kidney Disease, and Chapter 13: Causes and Treatment of Protein-Energy Wasting in Kidney Disease). Sarcopenia was initially described as occurring primarily from aging, and this has been referred to as *primary sarcopenia* [25]. However, in individuals with organ failure, such as in CKD, sarcopenia may occur in younger adults, independently of the aging process. Therefore, the European Working Group on Sarcopenia in Older People (EWGSOP) suggests the use of the term *secondary sarcopenia* when it is due to causes other than aging [25]. PEW and sarcopenia share many interlinked etiologic factors and diagnostic criteria; both are associated with poor clinical outcomes [26].

Frailty is a disorder commonly associated with PEW and sarcopenia (see Chapter 12: Assessment and Risk Factors for Protein–Energy Wasting and Frailty in Chronic Kidney Disease). Frailty is defined as a physiologic state of increased vulnerability to stressors that results from decreased physiologic reserves or dysregulation of multiple physiologic systems [26]. The clinical importance of frailty is that it is associated with poor clinical outcomes, due to a state of increased vulnerability, disability, dependence, falls, and institutionalization. Hence, frailty often results in hospitalization, poor quality of life, and increased risk of death. Frailty shares several common etiologic factors, criteria, and outcomes with PEW and sarcopenia [26]. The interconnection among these conditions is summarized in Fig. 32.1.

Obesity

Obesity is another common nutritional disorder in PD [5,11–13]. Most studies assessing its prevalence used BMI of 30 kg/m^2 or greater as the indicator of obesity (as proposed by the World Health Organization). However, although BMI is simple and useful, it is highly influenced by the hydration status, and, therefore, may misdiagnose individuals with fluid retention as being obese. In addition, BMI cannot differentiate between the lean body mass and fat mass components of body weight and is not able to evaluate the distribution of body fat [27]. The limitations of using BMI as an obesity marker might have contributed a debate whether obesity is a protective factor for mortality.

The so-called obesity paradox, much discussed in the early 2000s, refers to the association between an increased body weight for height, or elevated BMI, and a lower hazard ratio for mortality in chronic dialysis patients. This relationship was first described in the late 1990s [28] and has been confirmed subsequently in HD patients [29]. Of note, Kalantar-Zadeh et al. [30] reported that HD patients with body fat mass between 24% and 36%, estimated from rear-infrared reactance, had lower risk of mortality when compared to those



Common Etiological Factors

Increased protein catabolism
Inflammation
Activation of the ubiquitin-proteasome pathway,
Intercurrent catabolic illnesses (peritonitis, hyperparathyroidism)
Nutrient losses into the dialysate,
Resistance to anabolic hormones

Muscle disuse
Sedentarism

Low energy and food intake
Decreased appetite
Glucose absorption from the dialysate
Increased intra-abdominal pressure

Common Outcome

Low quality of life
Increased falls/fractures
Increased hospitalization rate
Increased mortality

FIGURE 32.1 The common etiologic factors, criteria, and outcomes among protein energy wasting (PEW), Sarcopenia and Frailty are illustrated in this figure (Venn diagram). Of note, low muscle mass is a common diagnostic criteria for the three conditions.

with body fat below 12%. Moreover, in a subgroup of patients subsequently assessed after 6 months, a body fat gain greater than 1% was associated with lower mortality risk when compared to patients that had a decrease of more than 1% of body fat [30]. However, more recently, in a cohort of 5904 incident HD patients, the mortality risk was reduced in patients with a high BMI who had inflammation, but not in those who did not have inflammation [31], suggesting that reduced mortality risk may depend on whether inflammation is present. In PD patients a relation between high BMI and lower mortality risk was observed in some studies [12,32], but not in others [13,33,34]. The different length of follow-up, prevalence of diabetes, cardiovascular disease, the presence of persistent inflammation, and distinct levels of solute clearance in these studies might account for these conflicting findings.

While one can make a cogent argument that ESRD patients should not be allowed to become markedly obese or remain obese, several studies suggest that obesity is epidemiologically associated with reduced mortality in ESRD patients. However, Ramkumar et al. [35] found that the amount of muscle mass, rather than BMI, was associated with lower mortality in PD patients. That said, although increased BMI is epidemiologically associated with reduced mortality, obesity should not be understood as a protective factor for PD patients, but rather—and especially abdominal obesity—as a condition that can lead to other disorders, including metabolic syndrome, cardiovascular disease, inflammation, faster decline in residual renal function, and longer time to kidney transplantation [12,34,35]. In fact, Obi et al. [12] have reported in a large cohort of PD patients that higher BMI was associated with shorter intervals until HD transfer, longer time to kidney transplantation, and although not significant, a tendency toward higher frequency of peritonitis. Also of note, obese PD patients had faster decline in residual renal function and lower total Kt/V [36]. In addition, some studies have shown that PD patients with higher body weight and body fat gains after initiation of PD showed more unfavorable metabolic results, such as increase in blood pressure, edema, obesity, diabetes, and metabolic syndrome than those with lower body weight and less body fat gain [36,37].

The increase in body weight and body fat in PD seems to be more pronounced in the first year of treatment, and the risk factors associated with this finding are increased age, diabetes, high BMI, and genetic polymorphisms of the uncoupling proteins 1 and 2 [36–40]. An involuntary energy input from the glucose absorption in the dialysate could also be implicated, but no clear association has been found between higher glucose absorption and body weight and body fat gain [5,36,39,40]. Altogether, it seems reasonable that obese patients undergoing PD with obese-related metabolic disorders and impaired quality of life should receive medical counseling with life-style changes, such as guided modification in dietary intake to their energy and protein needs and increased physical activity. The aim should be to ameliorate the metabolic disorders due to excessive body fat. Interventional studies testing the effects of these interventions in PD patients are still lacking. However, several studies, including randomized trials, demonstrate that the replacement of one exchange per day of a glucose-based dialysate with icodextrin-based dialysate resulted in a reduced body weight in the icodextrin group, whereas the patients using only glucose-based dialysate increased their body weight due to increased fat mass [41–43].

Assessment of nutritional status in peritoneal dialysis patients

Due to the nutritional disorders commonly observed in PD, careful regular nutritional assessments are warranted. They should start when the patient is beginning dialysis and continue periodically throughout the course of PD treatments. The revised Kidney Disease Outcome Quality Initiative (KDOQI) Clinical Practice Guidelines for Nutrition in CKD [44] recommend the use of composite methods for evaluation, such as the SGA and the malnutrition inflammation score (MIS), to assess nutritional status and to screen for PEW in PD patients. These methods consist of a questionnaire with two sections, in which the first one evaluates the following domains of nutrition status: spontaneous loss of body weight, changes in appetite, gastrointestinal symptoms, occurrence of comorbidities, functional status, changes in dietary intake (amount and consistency) as well as current dietary intake, while the second section includes a careful physical examination, including assessment of fat stores, muscle loss, and the presence of edema [45]. The questionnaire is scored according to the clinical judgment of the examiner which preferably is performed by a dietitian. But other health-care practitioners, such as nephrologists and nurses, can also be trained to conduct this examination [45]. However, since these are subjective methods (and do not screen for obesity), it is desirable to complement SGA and MIS with objective methods that assess body composition, food intake, biochemical alterations, and muscle strength (Table 32.4).

Ideally, a complete nutritional assessment is performed at the beginning of the PD treatment and periodically as needed, except for body weight, which is usually recorded daily by the patients to assess the

TABLE 32.4 Suggested methods and their strengths and limitations to assess nutritional status in peritoneal dialysis patients.

Method	Strengths	Limitations
Composite methods **1.** Subjective global assessment **2.** MIS	Provide assessment of five domains of nutritional status, ease of use, low cost, good predictive association with mortality and can be performed by trained clinical practitioners.	The scoring system is subjective to clinical judgment; large intra- and interexaminer variability; requires training; not suitable for screening for minor nutritional changes, or obesity. For MIS: uses laboratorial measurements and has no defined cutoff to classify malnutrition.
Body composition **1.** Anthropometry **2.** BIA (single or multifrequency)	Fast, low-to-medium cost, portable equipment, suitable for clinical practice.	Low-to-medium precision, subjected to intra- and interexaminer variability, influenced by hydration status. BIA: Measurements should be preferably made without dialysate in the peritoneal cavity. Results vary depending on the body composition software used in the equipment.
3. DXA **4.** CT **5.** MRI	Good precision, assessment of fat distribution. DXA and MRI: provide measurements of whole-body composition as well as from body segments. CT and MRI: provide measurements of subcutaneous and visceral fat as well as intramuscular fat. Not influenced by fluid status.	High cost for acquiring and maintaining the equipment, requires technician to perform the exam, suitable for research setting. DXA: The assessment of lean mass is influenced by the hydration status. Therefore it should be preferably performed without dialysate in the peritoneal cavity. CT: exposure to radiation.
Food intake **1.** 24-h food questionnaire **2.** Food registry **3.** Food history	Allows assessment of energy and nutrient intakes, food habits, food preferences, and aversions. Provides assessment of dietary quality and type of protein.	Subject to the patient's willingness to carefully report and remember food intake, difficult to estimate portion servings, estimation of energy, and nutrients are often underreported.
4. PNA	Objective method to estimate protein intake. Not subjected to patient under- or overreporting food intake.	Do not reflect protein intake if the patient is in a catabolic or anabolic state. Does not allow assessment of quality and type of protein ingested.
Biochemistry **1.** Serum albumin **2.** Serum CRP	Considered markers of inflammation with good prediction for mortality. CRP is a good marker of cardiovascular disease.	Albumin: Long median life; does not reflect nutritional status if inflammation is present or if there are large albumin losses into the dialysate (primarily if peritonitis is present). If hypervolemia is present, serum albumin values may be reduced due to dilution rather than to inflammation or protein-energy wasting.
Muscle function Handgrip strength (handgrip dynamometer)	Measurement of muscle function, included in the criteria to diagnose sarcopenia and frailty, highly correlated with muscle mass, a good predictor of hospitalization and mortality.	Does not reflect whole-body strength.

BIA, Bioelectrical impedance analysis; *CRP*, C-reactive protein; *CT*, computed tomography; *DXA*, dual energy X ray absorptiometry; *MIS*, malnutrition inflammation score; *MRI*, magnetic resonance imaging; *PNA*, protein equivalent of nitrogen appearance.

need for ultrafiltration, and recommended by the updated Nutrition KDOQI guidelines to be assessed at least monthly as part of the follow-up of nutritional status [44]. Our clinical experience indicates the need for a complete nutritional assessment at least once every 6 months to screen for early changes in nutritional status. Of importance for PD patients, assessment of body weight, waist circumference, and body composition should be performed with their peritoneal cavity empty so that dialysate fluid will not influence the measurements.

Nutritional counseling and recommendations for peritoneal dialysis patients

Patients undergoing PD treatment should receive specialized dietary counseling aiming to prevent and treat the nutritional disturbances commonly observed in this group of patients. Table 32.5 describes recommended energy, protein, and mineral intakes for PD patients according to different guidelines and consensuses [44,46]. For the dietitian in clinical practice the main challenge is to convert these recommendations

TABLE 32.5 Energy, nutrients, mineral, and liquids recommendations for peritoneal dialysis patients.

Energy/nutrient/ mineral	Recommendation	Reference
Energy (kcal/kg/day)	25–35[a]	[44]
Protein (kcal/kg/day)	1.0–1.2	[44]
	1.2–1.5	[46]
Potassium (mg/day)	Individualized to maintain serum potassium within the normal range. If hyperkalemia is present, consider lowering the dietary potassium intake to 2000–2500 mg/day	[44] [46]
Phosphorus (mg/day)	Individualized to about 800–1000 mg/day to maintain serum phosphorus within normal range	[44] [46]
Sodium (g/day)	<2.3	[44]
	1.8–2.5	[46]
Liquids (mL/day)	1000 + daily urine volume	[46]

[a] *Individualized according to the patient's nutritional status and physical activity. The energy derived from the glucose absorbed from peritoneal dialysate should be considered part of the total prescribed daily energy intake as described in Box 32.1.*

BMI, Body mass index.

# For body weight: use the patient's current body weight (after drainage of fluid from the peritoneal cavity) if it is thought to be indicative of adequate nutritional status. If not, the body weight within a BMI range of 23–29.9 kg/m2 is suggested by the authors due to the ease-of-use in clinical practice.

into a meal plan that is feasible for the patient and which, therefore, addresses such important aspects as socioeconomic and cultural factors and food habits and preferences. To achieve this goal the presence of a renal dietitian on the team that can dedicate the necessary time for planning, educating, and monitoring the patient during treatment is warranted [44].

Unfortunately, not all dialysis centers have the possibility to provide this kind of nutritional care, and low-dietary adherence is commonly reported. This has been shown in a metaanalysis assessing nonadherence to PD regimens (dialysis procedures, medication, and dietary fluid/restrictions). Of note, nonadherence to dietary fluid/prescription varied from 15%–67%, with a self-reported nonadherence to fluid restriction of 34%–56% [47]. Aligned with these findings, a study using 7 day–weighed dietary records, that is, food diaries where food to be ingested for a determined period are weighed using a kitchen food scale to improve precision in the portions recorded, showed that the mean energy and protein intake of PD patients was 25.3 ± 7.4 kcal/kg and 0.92 ± 0.36 g/kg (mean ± SD), which is lower than that recommended in the nutritional guidelines [48]. It is important to mention that these patients had a mean ratio of energy intake to resting energy expenditure of 1.22, meaning they were "good reporters" of their food intake. The factors associated with this nonadherence are diverse and include sociodemographic characteristics, medical treatment–related, issues and the number of individual contacts with health professionals [48]. To reduce the high rate of nonadherence to medical nutritional therapy, the use of a multidisciplinary and interdisciplinary team is desirable. Some of the specific issues relevant for PD patients are described later.

Energy and fat

According to the updated Nutrition KDOQI guidelines [44], ESRD patients should be advised to follow a diet with 25–35 kcal/kg of body weight/day, depending on age, level of physical activity, body composition, weight status goal, and the presence of inflammation to maintain adequate nutritional status. For PD patients the involuntary energy input derived from the glucose absorbed from the dialysate should be taken into account. When estimating the energy needs of patients with either insufficient energy intake, spontaneous body weight loss, or PEW and sarcopenia, it is recommended not to deduct from the estimated total energy needs the energy derived from glucose absorbed from dialysate. However, if the patient is overweight or obese, not under body weight loss or with adequate energy intake, the involuntary energy load from the glucose absorption from the dialysate can be discounted from the estimated total energy needs.

The energy load derived from the glucose in the dialysate varies depending on the dialysis modality (CAPD or APD) and differences with regard to the frequency of exchanges and total volume of dialysis fluid used (thus there is usually a higher glucose load with APD), glucose concentrations of the infused dialysis fluid, and also patient factors such as peritoneal transport status (fast/high transporters have more rapid absorption), and need for ultrafiltration [49]. However, the percentages of the instilled amount of glucose that is absorbed from the three different dialysis fluids (1.36%, 2.27%, and 3.86%) in CAPD patients were, on average, almost identical, 63% and 75%, respectively, after 240 and 360 minutes: after a dwell time lasting 6 hours, the initial amount of intraperitoneal glucose absorbed corresponded to a mean (± SD) energy supply of 75 ± 6, 131 ± 18, and 211 ± 26 kcal for the three solutions (1.36%, 2.27%, and 3.86%), respectively [49]. In a study from Grodstein et al. [50], the daily energy supply in CAPD patients from dialysate glucose was 8.4 ± 2.8 kcal/kg (mean ± SD) of body weight per day, or 12%–34% of total energy intake. Table 32.6

TABLE 32.6 Glucose concentrations and corresponding energy load in glucose-based peritoneal dialysis fluids, and the estimated energy input from glucose absorption from the dialysate.

Solution	Glucose monohydrate (g/L)	Glucose anhydrate (g/L)	mmol/L	Total energy load[a] (kcal/L)	Energy from glucose from a 2-L bag[b]
1.5%/1.36%	15	13.6	75.5	50	70 kcal/2 L
2.5%/2.27%	25	22.7	126	84	118 kcal/2 L
4.25%/3.86%	42.5	38.6	214	143	201 kcal/2 L

[a] *0.67 kcal/mmol of anhydrous glucose.*

[b] *Assuming that 70% of glucose is absorbed.*

Please note that in some locations, including the United States, glucose content is expressed as the amount of glucose monohydrate (molecular weight 198.17 g/mol), whereas in Europe and other locations the amount of anhydrous glucose (molecular weight 180.156 g/mol) is stated (multiply dextrose monohydrate by 0.909 to obtain the amount or concentration of anhydrous dextrose). The corresponding concentrations are given earlier. The energy equivalent for glucose monohydrate is about 3.4 kcal/g and for anhydrous glucose about 3.7 kcal/g. On average, about 70% of the infused glucose is absorbed after 4–6 h during CAPD but differs according to the duration of the dialysis fluid exchange (63% at 4 h and 75% at 6 h), the patient's peritoneal transport group (higher absorption in fast/high transport patients), and other factors [49,51]. *CAPD*, Continuous ambulatory peritoneal dialysis.

BOX 32.1

Example of how to calculate the estimated glucose absorption for a patient under treatment with continuous ambulatory peritoneal dialysis (CAPD) or automated peritoneal dialysis (APD).

CAPD

1. Collect information on dialysis prescription of the patient. Example:
    3 bags of 2 L with 1.5% of glucose monohydrate (13.6 g/L of anhydrous glucose; multiply dextrose monohydrate by 0.909 to obtain the amount or concentration of anhydrous dextrose)
    1 bag of 2 L with 4.25% of glucose (38.6 g/L of anhydrous glucose)
    Observation: Note that the dialysis fluid bags usually are slightly overfilled, and the overfill should be assessed for the brand of dialysis fluid used
2. *Calculate total glucose content according to the information described in* Table 32.6
    6 L × 75.5 mmol/L = 453 mmol
    2L × 214 mmol/L = 428 mmol
    Total amount infused = 453 + 428 = 881mmol
3. *Measure drained volume and glucose in drained dialysate*
    Example drained volume 8750 mL and glucose concentration in drained dialysate 31 mmol/L gives drained glucose amount 8.75 L × 31 mmol/L = 271 mmol/L
4. *Calculate amount of glucose absorbed and corresponding energy*
    881 − 271 mmol = 610 mmol = 610 × 0.67 kcal = 409 kcal

APD

1. Collect information on dialysis prescription of the patient. Example:
    The volume of the infused dialysis solution is given by the APD cycler
2. Calculate the total infused glucose
    a. Multiply the total volume in L by the glucose concentration as earlier for CAPD
    b. Sum up the total amount of glucose infused, as earlier for CAPD
3. Calculate the amount of glucose absorbed by measuring glucose in drained dialysate or approximate it to 30%–50% but differ due to dialysate flow rate, and the patients peritoneal transport group A mean of 40% could be used as an estimation of the glucose absorbed
4. Calculate the estimated corresponding energy load (kcal/day)

describes the glucose amount, energy load, and estimated energy input from the glucose absorption according to the glucose concentration in the solution. Box 32.1 describes an example on how to calculate the estimated glucose absorption for a patient undergoing CAPD or APD.

Regarding fat intake, although there is no specific recommendation for PD patients, it seems reasonable to follow the recommendations from the American Heart Association dietary guidelines to control the plasma lipid profile [52]. According to this guideline, the total dietary fat should provide 25%–35% of the total energy intake in which <7% of the energy is from saturated fat, more than 20% from monounsaturated fatty acids, and more than 10% of energy from polyunsaturated fatty acids (PUFA). The total intake of cholesterol should be <200 mg/day. In addition, the updated Nutrition KDOQI Guidelines recommend supplementation with 1.3–4 g/day of PUFA to improve the lipid profile [44].

Regarding dialysate protein-energy supplementation, the updated Nutrition KDOQI Guidelines [44] do not suggest substituting dextrose dialysate with amino acid dialysate as a general strategy to improve nutritional status. However, if energy and nutritional intake (by oral or enteral intake) is below the nutritional requirements, the use of peritoneal dialysate that contains 1.1% of amino acids may be considered to diminish protein deficits, as suggested in previous studies where an increase in serum albumin and anthropometric measurements of muscle mass were found in malnourished patients with the use of dialysate containing amino acids [53,54]. These findings were reported in randomized controlled studies in CAPD patients, in which one exchange of 1.5% dextrose dialysate was replaced by 1.1% amino acid dialysate daily from 3 months to 3 years [53,54]. It is important to mention that dialysate with amino acids is not available in many dialysis centers and, therefore, may not a feasible clinical alternative.

Protein

With respect to recommended dietary protein intakes, metabolic studies indicate that a protein intake of about 1.1 g/kg/day may be necessary to ensure neutral or positive nitrogen balance in virtually all clinically stable adult PD patients (as long as enough energy is provided) [21,55,56]. These data are consistent with other guidelines or consensus statements that the estimated protein needs of adult PD patients may vary from 1.0 to 1.4 g/kg/day [44,46]. Despite these variations in dietary protein recommendations, metabolic studies show that most patients can maintain neutral nitrogen balance with a protein intake close to 1.0 g/kg/day [21,55]. In theory, the dietary protein requirements of PD patients should be the same as for healthy individuals plus an added amount of protein corresponding to the increased nitrogen losses in the dialysate. These losses may be further enhanced by inflammatory and catabolic stimuli linked to the dialysis procedure (effect of the dialysate and catheters and especially if there are episodes of peritonitis) and to the numerous metabolic disturbances common in ESRD patients. Since the average loss of protein into dialysate is about 5–15 g/day [57], the daily protein intake of a PD patient needs to be increased by around 0.1–0.2 g protein/kg/day for an adult weighing 60 kg. Therefore, at least in theory, the total protein requirements for PD patients would be approximately 1.0–1.2 g/kg/day. On the other hand, a high protein intake could make the control of phosphorus levels more difficult and might worsen the complications resulting from hyperparathyroidism, elevated FGF-23 levels, and a high plasma calcium–phosphorus product (see Chapter 17: Disorders of Phosphorus Homeostasis: Emerging Targets for Slowing Progression of Chronic Kidney Disease, Chapter 23: Calcium, Phosphate, PTH, Vitamin D, and FGF-23 in CKD-Mineral and Bone Disorder, and Chapter 24: Phosphorus Metabolism and Fibroblast Growth Factor 23 in Chronic Kidney Disease). Therefore the current recommendation from the updated Nutrition KDOQI Guidelines of 1.0–1.2 g/kg of body weight/day should provide an adequate amount of protein to cover the protein needs for most clinically stable PD patients while taking into consideration the amount of protein intake that is compatible with adequate phosphorous control [44].

Phosphorus

This subject is discussed in Chapter 17, Disorders of Phosphorus Homeostasis: Emerging Targets for Slowing Progression of Chronic Kidney Disease, Chapter 23, Calcium, Phosphate, PTH, Vitamin D, and FGF-23 in CKD-Mineral and Bone Disorder, and Chapter 24, Phosphorus Metabolism and Fibroblast Growth Factor 23 in Chronic Kidney Disease, and can be used to further complement information on phosphorus metabolism, physiology and needs in this group of patients. A careful balance between the need to increase protein intake while restricting phosphorus intake should be considered when counseling PD patients with regard to diet, since most food sources of protein are also rich in phosphorus. A well-known dietary strategy to achieve the protein needs and, at the same time, not exceed the phosphorus intake is to educate patients regarding dietary choices [58]. The following can be advised:

1. To prevent or treat hyperphosphatemia, foods that have a high phosphorus (mg)-to-protein (g) ratio should not be eaten in large amounts. In general, dairy products (milk, yogurt, and cheeses), some types of meat (such as liver and other viscera), and some fishes (such as sardines) are examples of foods with a high phosphorus:protein ratio [57]. Those foods should not be excluded from the diet but rather ingested in small-to-moderate servings. It is also important to consider that the bioavailability of phosphorus from animal protein is higher than that from vegetable protein, indicating that there is a

higher absorption of phosphorus from animal protein in the gastrointestinal tract. In vivo studies show that gastrointestinal digestion and absorption varies from 53% to 78% of the phosphate in dairy products, from 73% to 89% of the phosphate in red meat and poultry, and less than 50% of phosphate in vegetables [59,60]. The explanation for this difference is that most phosphate in vegetables is bound to phytate, which is not well digested by humans due to the lack of the enzyme phytase in the intestine [61]. That said, vegetable protein can also be considered as a preferred source of protein in people with severe hyperphosphatemia.

2. If hyperphosphatemia is present, phosphorus-rich food sources especially those that are not rich in protein, such as beer, soft "cola" drinks, and chocolate, but also peanuts, other nuts, peanut butter, and almond butter, can be replaced with other foods with low phosphate content [58].
3. Finally, many additives used in processed and ultraprocessed food to increase shelf time and prolong the expiration date are composed of inorganic phosphate. A higher proportion of inorganic phosphate is absorbed by the gastrointestinal tract, and, therefore, the intake of processed foods containing inorganic phosphate provides a "hidden" source of phosphate that should be avoided [58]. Educating patients to read food product labels is a valid strategy to diminish the serum phosphorus level [62].
4. If phosphate binders are used to control hyperphosphatemia, it is important to combine its use at the times of meals that contain larger food sources of phosphorus, since the phosphate binders act in the gastrointestinal tract by forming a poorly absorbed, insoluble compound that is eliminated in the feces [58]. To increase the adherence to the prescribed dosage of phosphate binders, it is important to explain to patients how they work.

Potassium

Dietary restriction of potassium is one of the most common foci of nutritional counseling for CKD and ESRD patients. The concern over hyperkalemia has led some clinical practitioners to the view that all high potassium foods (mainly fruits, vegetables, grains, and nuts) should be avoided. However, since these foods can contain substantial amounts of fiber, vitamins, and antioxidants, one should evaluate more carefully whether avoidance of these foods is indeed necessary. Restricting these food items can be harmful since this practice may generate a poor-quality diet with a reduced fiber content. This, in turn, can engender intestinal disorders, including constipation, and an unhealthy gut microbiota that may increase plasma concentrations of proinflammatory cytokines [17,63,64].

In fact, a study, including PD patients, reported that 90% of these patients had a low-dietary intake of fiber (median fiber intake, 12.2 g/day). Patients with a fiber intake above the median (>12.2 g/day) had significantly lower intraperitoneal levels of proinflammatory cytokines. However, in serum, only the cytokine monocyte chemoattractant protein-1 was lower than in the group with fiber intake below the median (<12.2 g/day) [64]. Moreover, a recent study showed that dietary fiber [mean intake, 8.2 ± 3.4 g/day (± SD)] was associated with lower all-cause mortality in nondiabetic PD patients [65]; however, further studies are needed to establish whether the fiber intake and lower mortality are causally related.

Therefore some conditions should be considered before restricting dietary sources of potassium: first, dietary potassium should be restricted only if hyperkalemia is present, which is not the case for all PD patients; hypokalemia (<3.5 mEq/L) is almost as prevalent as hyperkalemia (>5.0 mEq/L) in PD patients [66].

Second, even if hyperkalemia is present, it is important to investigate whether the patient has a high intake of potassium. Hyperkalemia can be caused by many factors, including decreased renal function, metabolic acidosis, hyperglycemia, intestinal constipation, use of renin–angiotensin–aldosterone system inhibitors, and low dialysis adequacy [63]. Therefore high dietary potassium intake may not be the cause of hyperkalemia, and potassium restriction may not treat the underlying condition and could lead to a harmful, poor-quality diet.

Third, if the patient has hyperkalemia and there is an increased potassium intake, there are fruits and vegetables with lower potassium content (<200 mg/serving) that can be counseled to replace those with higher potassium content (Table 32.7). In addition, cooking vegetables in boiling water, with the vegetables unpeeled, and draining the water after they are cooked is a simple procedure that can diminish up to 80% of the potassium content of vegetables [67]. Although this procedure diminishes the content of water-soluble vitamins, it is still a valid procedure to allow the intake of vegetables in the diet of patients with hyperkalemia.

Finally, potassium additives are increasingly used not only in ultraprocessed foods but also in processed foods to diminish or replace sodium chloride [68]. Processed food refers to any food that has been processed by food industry and may, therefore, include uncooked food (as an example, uncooked meat, poultry, or fish; refined grains and other foods that are processed for packing purposes). Similar to phosphate,

TABLE 32.7 List of fruits and vegetables with low and high content of potassium per serving.

Fruits	Raw vegetables
Fruits and vegetables with low potassium content (<200 mg/serving)	
1 medium persimmon	5 lettuces leaf
1 medium slice of pineapple	1 cup of watercress
10 small strawberries	1 cup of sliced cucumber
1 medium apple	1 cup of cabbage
1/2 of medium mango	3 radishes
1 medium pear	1 medium paprika
1 medium peach	1 tomato
1 medium fresh plum	1/2 of medium carrot
1/2 cup of blueberry	1/2 cup of escarole
40 mL of lemon juice	
Food with high potassium content (>200 mg/serving)	
1 medium banana	1 cup of kale
1 slice of melon	3 spoon soups of beet
1 orange	2 tomatoes
1 tangerine	1 cup of broccoli
1 kiwi	
1/2 avocado	
coconut water from 1 coconut	
1 cup (cubes) of papaya	
10 grapes	
1 cup of cherries	
3 passion fruits	

potassium additives are a “hidden” source of potassium that is highly absorbed in the gastrointestinal tract [68]. Therefore foods with potassium additives should be restricted from the diet of PD patients. Star fruit, however, should be prohibited altogether from the diet of patients with ESRD not due to its potassium content, but due to a neurotoxin present in the star fruit that cannot be well depurated by dialysis [69]. Depending on the amount of star fruit eaten, intoxication can occur with symptoms of intractable hiccups, mental confusion, prolonged seizures, and, in severe cases, death [69].

Fluids and sodium

Since PD is performed for many hours each day, it should be possible to obtain better fluid control than with HD patients. The fluid prescription (restriction) should be individualized according to the patient’s urine output (if present) to maintain adequate fluid control with no edema. To achieve this, it is important to encourage patients to follow a low-sodium diet with very limited intake of ultraprocessed food (such as sausages, processed cheeses, chips, ready-to-go foods). The use of herbs and spices to replace or diminish the use of salt is a feasible maneuver to enhance taste and increase adherence to a low-sodium diet. Of importance, patients should be reminded not to use potassium chloride to replace regular salt (sodium chloride) when cooking, as this can increase serum potassium as mentioned before.

Which body weight should be used to calculate energy and protein recommendation?

The determination of body weight is a central consideration for diet prescription. The desirable body weight which is used to calculate the dietary prescription is often calculated as the weight which is consistent with the patient’s normal BMI or the patient’s usual or current body weight. According to the updated Nutrition KDOQI Nutrition in CKD guidelines [44], the desirable body weight can be determined by clinical judgment concerning the patient’s health goals. It is important to evaluate whether the patient’s current body weight (without fluid in the peritoneal cavity) is indicative of adequate nutritional status. If so, the current body weight can be used to calculate the dietary prescription. However, if the current body weight is indicative of obesity (e.g., a BMI $\geq 30\ \mathrm{kg/m^2}$) or if the nutritional status is indicative of mild-to-severe malnutrition (according to SGA or MIS or BMI $<23\ \mathrm{kg/m^2}$), the body weight that reflects a BMI of $23-29.9\ \mathrm{kg/m^2}$, and which is closest to the patient’s usual body weight, has been proposed as the weight to be used for dietary prescription. The most important criteria for deciding the desirable body weight should be the patient’s nutritional condition and health goals.

Healthy diet for peritoneal dialysis patients: an important concept that has been neglected in the renal diet

As a first principle for the dietary prescription for PD patients, the diet should be healthy. This means that the diet should enable long-term health. In addition to an adequate intake of macronutrients (protein, fat, and carbohydrates), and essential minerals and micronutrients (vitamins and trace elements), patients may benefit from the intake of bioactive nutrients; that is, nonessential biomolecules present in foods that exhibit the capacity to modulate metabolic processes, thereby contributing to better health. Examples of such compounds are the phytochemicals (present in small amounts in plant foods such as fruits, vegetables, and grains) that may have beneficial effects by reducing inflammation, senescence, mitochondrial dysfunction, gut dysbiosis, and improving one-carbon metabolism. Taking into account the "foodome" (a new area of food science and nutrition aiming to analyze the effects of food on human health) and using "food as medicine" are new approaches likely to play an important future role to prevent the progression of kidney disease and reduce the risk of its complications [70]. A diet with many restrictions, with very limited intake of fruits, vegetables, grains, whole cereals, and nuts, is in direct contrast to a healthy diet and can induce the patient to follow a poor-quality diet with an increased intake of highly processed foods. Unnecessary dietary restrictions, such as unjustified restriction of food sources of potassium, should be discouraged. Instead, a careful meal plan that includes all food groups (cereals, mainly whole cereals; grains; fruits and vegetables; nuts; meat, preferably fish and poultry; eggs; vegetable; and fish oil) is encouraged.

Observational data suggest that patterns of chronic food intake similar to the Mediterranean Diet and the DASH Diet (Dietary Approach to Stop Hypertension) may reduce the incidence of CKD, decrease the progression of CKD to ESRD, and reduce mortality rates in CKD and maintenance HD patients [71–73]. These diets are characterized by a high intake of fruits, vegetables, grains, whole cereals, and moderate intake of lean meat (poultry and fish), eggs, and low-fat dairy products (milk, yogurt, and cheese). Although studies investigating the role of a healthier dietary pattern in PD patients are lacking, it seems reasonable to conclude that patients on PD may also benefit from such healthy dietary patterns.

As is emphasized in this chapter, even when dietary restriction of phosphorus and potassium are needed, dietary counseling should include healthy foods. Priority should be given to restricting processed foods that contain hidden sources of four undesirable elements of the renal diet: inorganic phosphate and potassium, which are both highly absorbed by the gastrointestinal tract, and sodium and poor-quality fat (i.e., saturated fatty acids, trans-fatty acids, and cholesterol). It is critical to encourage patients, family members, and/or the patient's caregiver to buy fresh ingredients, cook, and use the mealtimes as enjoyable daily events. These activities are the key for long-term adherence to healthy and appropriate renal diets.

Finally, the need for vitamin supplementation due to deficient intake, peritoneal losses, altered activity, inhibition, decreased intestinal absorption, or drug interactions should be considered and is addressed in Chapter 26, Vitamin Metabolism and Requirements in Chronic Kidney Disease and Kidney Failure.

Conclusion

PD patients require special attention regarding their food intake. The nutritional derangements that may occur as a result of the patient's disease states and PD treatment require careful assessment and monitoring of the patient's nutritional status. Similarly, dietary counseling that can formulate meal plans that meet and take into account the patient's individual nutritional needs, socioeconomic condition, cultural status, food preferences, and food habits is the key to facilitating dietary adherence. Also, highly important is close follow-up of the patient with frequent visits with a dietitian who is an integral part of the interdisciplinary renal team. With regard to medical nutritional therapy, there is no single rule that fits all patients. Rather, an individualized plan for nutritional assessment, planning the diet, training the patient, and follow-up of the patient is the key to achieving satisfactory results.

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C H A P T E R

33

Nutritional management of kidney transplantation

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Introduction

Kidney transplantation is a renal replacement therapy for patients with end-stage kidney disease (ESKD) that, when successful, largely corrects the metabolic abnormalities associated uremia and dialysis. However, side effects of immunosuppressive medications and posttransplant changes of lifestyle, together with perceived dietary freedom after successful transplantation, introduce a new set of metabolic challenges [1]. These may lead to clinical problems such as hypertension (HT), diabetes, dyslipidemia, and obesity. Together with preexisting comorbidities, these may negatively impact short- and long-term health outcomes for kidney transplant recipients (KTRs), including delayed graft function (DGF), acute rejection (AR), chronic allograft nephropathy (CAN), and reduced recipient and graft survival [2].

Nutritional challenges begin before kidney transplantation and change overtime after transplantation (Fig. 33.1). Emerging evidence suggests pretransplant nutritional status may affect posttransplantation outcomes, indicating that it is important to maintain optimal nutritional care during maintenance dialysis therapy and in preparation for transplantation. Posttransplant nutritional management is described in the previous chapter on nutritional management of kidney transplantation in the third edition of this book [3], from the evidence-based renal nutrition practice guidelines entitled, the Caring for Australasians with Renal Impairment (CARI) guidelines [4] and National Kidney Foundation Kidney Disease Outcomes Quality Initiative clinical practice guidelines for nutrition in chronic kidney disease (CKD) [5]. Over the years, additional evidence from observational and interventional studies on various aspects of management have supported the potential benefit of incorporating nutrition in the routine medical care of KTRs.

This chapter begins by reviewing the evidence that pretransplant nutrition is a determinant of posttransplant outcomes. We then review the currently available practice guidelines and new literature on nutrition posttransplantation, covering traditional and new topics such as dietary patterns and nutritional intervention trials, spanning from the acute posttransplant period, through the maintenance phase, and into the period of the failing graft. We conclude with a general, practical approach to the nutritional management of potential and established KTRs.

Pretransplant factors affecting posttransplant outcomes

Weight and body mass index

Nutritional abnormalities in KTRs, including those present pretransplant and those that develop after transplantation, may lead to undesirable outcomes that affect the quality of life, complication burden, and graft and patient survival. The World Health Organization (WHO) uses body mass index (BMI in kg/m^2) classifications to categorize body weight as underweight (<18.5), normal (18.5–24.9), overweight or preobesity (25.0–29.9), obesity class I (30.0–34.9),

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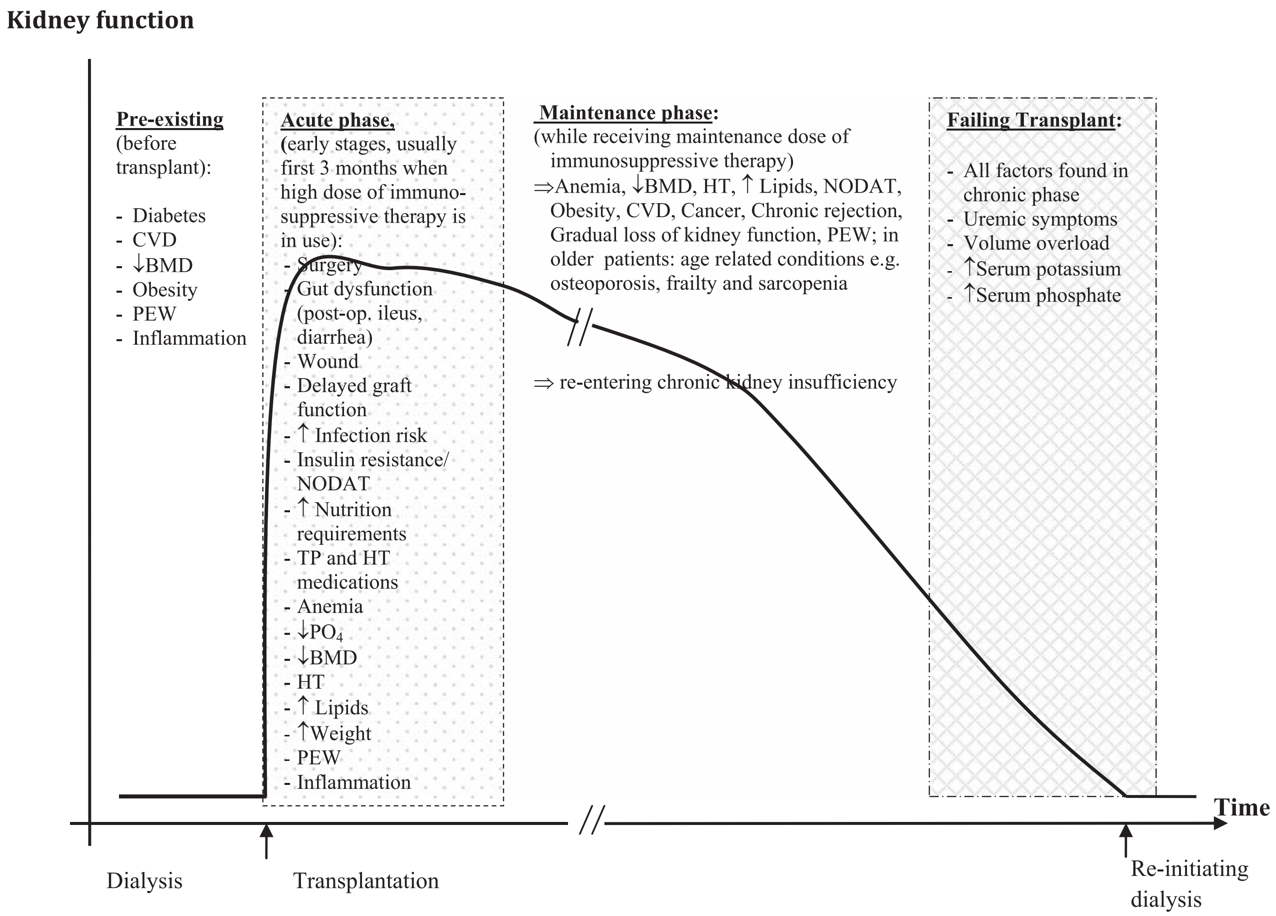
Kidney function
Pre-existing (before transplant):
- Diabetes
- CVD
- ↓BMD
- Obesity
- PEW
- Inflammation
Acute phase, (early stages, usually first 3 months when high dose of immuno-suppressive therapy is in use):
- Surgery
- Gut dysfunction (post-op. ileus, diarrhea)
- Wound
- Delayed graft function
- ↑ Infection risk
- Insulin resistance/ NODAT
- ↑ Nutrition requirements
- TP and HT medications
- Anemia
- ↓PO4
- ↓BMD
- HT
- ↑ Lipids
- ↑Weight
- PEW
- Inflammation
Maintenance phase: (while receiving maintenance dose of immunosuppressive therapy)
⇒Anemia, ↓BMD, HT, ↑ Lipids, NODAT, Obesity, CVD, Cancer, Chronic rejection, Gradual loss of kidney function, PEW; in older patients: age related conditions e.g. osteoporosis, frailty and sarcopenia
⇒ re-entering chronic kidney insufficiency
Failing Transplant:
- All factors found in chronic phase
- Uremic symptoms
- Volume overload
- ↑Serum potassium
- ↑Serum phosphate
Time
Dialysis
Transplantation
Re-initiating dialysis

FIGURE 33.1 Schematic diagram showing nutritional and related factors affecting kidney transplant recipients. *BMD*, bone mineral density; *CVD*, Cardiovascular disease; *HT*, hypertension; *NODAT*, new-onset diabetes after transplantation; *PEW*, protein-energy wasting; *TP*, information from kidney transplant specific study.

obesity class II (35.0−39.9), and obesity class III (40 or greater) [6]. In the general population, overweight and obesity are associated with increased morbidity and mortality risk. Therefore public health and WHO messages have always emphasized, in the general population, the importance of attaining a healthy weight. This message is almost certainly relevant to transplant candidates and recipients.

Underweight is a relatively uncommon problem among KTRs. However, registry studies have revealed powerful associations between low BMI and an increased incidence of posttransplant infection and mortality [7,8]. In one large US registry study, being underweight ($BMI < 18.5\ kg/m^2$, prevalence 3.8%) was associated with late graft failure [adjusted odds ratio (OR), 1.76; 95% confidence interval (CI), 1.16, 2.69; $P < .01$], mainly due to CAN [9]. Obesity is far more common among KTRs, particularly in Western countries. Obesity and the degree of obesity at the time of transplantation have been associated with both poorer early outcomes, including DGF, AR, wound healing disorders and new-onset diabetes, and long-term outcomes, including cardiovascular (CV) morbidity and mortality [2,7,9−11]. Moreover, weight gain is common after kidney transplantation, averaging about a 10%−20% gain in body weight, that occurs mostly during the first year after renal transplantation [12,13], which further negatively affects outcomes.

An important question is whether the presence of obesity should be taken into account when accepting candidates into the kidney transplant program. To examine the effects of obesity at the time of transplantation on outcomes, several studies compared nonobese ($BMI < 30\ kg/m^2$) and obese ($BMI \geq 30\ kg/m^2$) patients. The studies generally demonstrated inferior graft and patient survival among obese recipients [7,11,14,15]. However, in a larger and more sophisticated USRDS registry analysis, Gill et al. found that obese candidates who received a kidney transplant experienced significantly improved survival as compared to those who remained on the waitlist. A survival benefit was evident for all strata of obesity, including patients with $BMI > 40\ kg/m^2$, with the exception of African-Americans with $BMI > 40\ kg/m^2$ [16]. It should be emphasized that these findings are not in conflict with the other reports that outcome is superior in nonobese as compared to obese patients who receive a kidney transplant [7,11,14,15]. In a single Australian transplant center with a rigorous CV disease screening program for transplant candidates, the prevalence of obesity was found to be 12% (59/493) in transplanted patients over a 6-year period of study [11]. The 5-year survival analysis between the nonobese and obese groups did not show any significant difference for graft survival (83% vs 84%, $P=$NS) or patient survival (91% vs 91%, $P=$NS). For short-term outcomes, obese patients were more likely to experience superficial wound breakdown (14% vs 4%, $P<.01$) and complete wound dehiscence (3% vs 0%, $P<.01$) and tended to have a higher rate of wound infections (15% vs 8%, $P=.11$). No significant difference between the two groups was shown for operative duration, postoperative complications, hospitalization, DGF (or AR episodes. On multivariate analysis, BMI was found to be an independent risk factor for wound breakdown (OR, 1.21; 95% CI, 1.09−1.34; $P<.001$), but not for other posttransplant complications, hospitalization, graft loss, or patient survival.

With regard to intermediate outcomes, in an analysis of 5684 patients from the Australian and New Zealand Dialysis and Transplant registry, obesity was associated with greater odds for DGF (adjusted OR, 1.56; 95% CI, 1.23−1.97; $P<.001$) and 6-month AR (adjusted OR, 1.25; 95% CI, 1.01−1.54; $P<.04$) [7]. Other results were observed in a center in the United States, with 193 patients with >6 months of follow-up; there was an increased incidence of surgical complications in the obese kidney transplant recipients; however, these individuals did not show an increased rate of AR or graft or patient loss [14]. When comparing the outcomes of morbidly obese KTRs ($n=23$, BMI 37−56 kg/m^2) with nonobese KTRs ($n=244$, BMI 25 kg/m^2) at another US transplant center, the morbidly obese KTRs had more complications and a greater length of hospital stay (LOS), but there was no difference in the 3-year graft and patient survival [15].

Thus the current literature demonstrates that the major adverse effect of obesity on kidney transplant outcomes is an increase in wound or surgical complications, but graft function and graft and patient survival are not negatively affected by obesity. These findings suggest that obesity, and even morbid obesity, should not per se preclude access to kidney transplantation. These observations are supported by a systematic review and metaanalysis of 17 studies, including 138,081 patients that found obese patients have similar survival to recipients with normal BMI [hazard ratio (HR), 1.24; 95% CI, 0.90−1.70] [17].

BMI is crude measure of adiposity; for example, greater muscle mass may also increase the BMI. In a cohort of 10,090 hemodialysis-dependent transplant candidates, patients with healthier body composition, namely, those who had larger pretransplant muscle mass, as indicated by higher pretransplant serum creatinine levels, were found to have greater posttransplant graft and patient survival [18]. Consistent with this finding, the waist-to-hip ratio (WHR) has been reported to be more closely associated with posttransplant complications than the BMI [19].

Traditional research in this area has tended to focus on weight recorded at the time of study and its relationship with defined adverse outcomes. Weight "change" from pre- to posttransplantation has seldom been investigated. A patient's nutritional status while waiting for transplantation can change, whether it is intentional weight loss in obese patients that is intended to achieve an arbitrary BMI target for enrolling in the transplant program or unintentional loss due to intercurrent illnesses.

In retrospective analyses of 94,465 recipients of deceased donor kidney transplantation (DDKT) [20], the relationship between the weight change from the time of enlistment into the transplant program until transplantation was examined with regard to three outcomes: LOS posttransplant, all-cause graft failure, and mortality. Weight change was categorized into 5% increments: <5% change, ≥5%−<10% weight loss, ≥10% weight loss, ≥5%−<10% weight gain, and ≥10% weight gain. Median follow-up time posttransplant was 5.0 years [interquartile range (IQR), 3.1−7.7 years]. The nonlinear, unadjusted associations between relative pre-DDKT weight loss, longer transplant LOS, higher graft loss, and higher mortality were examined. The median weight change was 0 kg (IQR, −3.5 to +3.9 kg). However, 11% of patients lost >10% of their enlistment weight. Compared to those with <5% weight change pre-DDKT (52% of total studied subjects), these former patients had longer average transplant LOS by 0.66 days (95% CI, 0.23−1.09; $P=.003$), higher graft loss (adjusted HR, 1.11; 95% CI, 1.06−1.17; $P<.001$), and higher mortality (adjusted HR, 1.18; 95% CI, 1.11−1.25; $P<.001$) independent of their BMI or other recipients, donor, and transplant factors. The major limitations of this study were such unmeasured confounders as body composition, inability to identify volitional weight change, and the interactions between comorbid conditions and weight change.

In analyses of 632 transplant-waitlisted hemodialysis patients, mortality was predicted using the 13 week-averaged BMI, the pretransplant serum creatinine as a surrogate of muscle mass, and the changes in these variables overtime [8]. Each kg/m^2 increase in BMI was associated with a death HR of 0.96 (95% CI, 0.95−0.97); the lower 4th and 5th quintile of serum creatinine had an HR of death of 0.75 (95% CI, 0.66−0.86) and 0.57 (95% CI, 0.49−0.66), respectively. Patients with minimal weight change (< ± 1 kg) over 6 months had a lower death risk as compared to those whose weight decreased in the range of 3− < 5 kg (HR, 1.31; 95% CI, 1.14−1.52) and a weight loss of 5 or more kg (HR, 1.51; 95% CI, 1.30−1.75). This study showed that hemodialysis-dependent transplant candidates with a lower BMI or muscle mass and/or weight or muscle loss have higher mortality. Similar to the previous study, the effect of intentional weight change was not known. It should be remembered that people who ingest large amounts of meat (i.e., striated muscle) or creatine supplements, for example, for physical fitness, can increase their serum creatinine independently of changes in their muscle mass.

Given the rising prevalence of obesity among kidney transplant candidates and potential candidates, coupled with evidence that obesity imparts potential increased risks of short- and long-term posttransplant complications and costs, the pros [21] and cons [22] of pretransplant weight loss have been debated [23]. No clear answer is apparent. The association of pretransplant weight loss with the higher posttransplant mortality noted earlier, coupled with the costs of delaying transplantation to achieve weight loss through diet or other strategies, argue strongly in favor of transplanting patients regardless of their obesity status. Advances in surgery and posttransplant management and new immunosuppressive medications have reduced the risk of posttransplant complications and may render posttransplant strategies to lose weight safer than pretransplant attempts. Current literature is unable to definitively answer this debate.

Protein-energy wasting/malnutrition

In contrast to overnutrition, the presence of malnutrition, irrespective of body weight or BMI, is predictive of poor posttransplant outcomes. Serum albumin is a surrogate marker of protein-energy wasting (PEW) and inflammation in chronic dialysis patients and can predict poor posttransplant outcomes [24,25]. In a cohort of 8961 hemodialysis patients who underwent their first kidney transplantation, a higher last-3-month averaged pretransplant serum albumin was associated with lower risks of mortality, graft failure, and DGF [26]. For every 0.2 g/dL higher pretransplant serum albumin concentration, there was a 13% lower all-cause mortality (HR, 0.87; 95% CI, 0.82−0.93), 17% lower CV mortality (HR, 0.83; 95% CI, 0.74−0.93), 7% lower combined risk of death or graft failure (HR, 0.93; 95% CI, 0.89−0.97), and 4% lower DGF risk (OR, 0.96; 95% CI, 0.93−0.99). A pretransplant serum albumin level that was in the lower quintile (<3.77 g/dL) was associated with worse short- and long-term posttransplant outcomes.

The malnutrition, inflammation, and atherosclerosis (MIA) syndrome is associated with a high mortality rate in dialysis patients [27,28]. In a retrospective study of 1348 adult KTRs [29], the occurrences of posttransplant fatal and nonfatal acute coronary syndromes (ACS) were analyzed in relation to the pretransplant MIA factors: malnutrition (serum albumin, cholesterol and BMI), inflammation (C-reactive protein level), and atherosclerosis (history of CV, cerebrovascular or peripheral vascular disease). Patients with a higher pretransplant MIA score, which indicates more severe protein−energy malnutrition and/or inflammation, showed worse outcomes of ACS ($P < .001$) and composite outcomes of ACS and all-cause mortality ($P < .001$) than those patients with a lower pretransplant MIA score. Compared with the lowest MIA-scoring group, the highest MIA-scoring group had a higher incidence of ACS (HR, 6.12; 95% CI, 1.84−20.32; $P = .003$). The presence of MIA factors pretransplant, is therefore, an independent predictor of posttransplant CV outcomes.

Glycemic control

As a nutrition-related metabolic disease, diabetes mellitus is associated with poor outcomes in the general, dialysis and transplant populations. Diabetes present before transplantation [30] and diabetes developing after transplantation [31] are both strongly associated with worse posttransplant outcomes, and with increased CV morbidity and mortality, in particular. The importance of glycemic control in those with diabetes is less well known. In a 6-year follow-up study of a cohort of 2872 diabetic dialysis patients who underwent their first kidney transplantation, the dose−response association between pretransplant glycemic control [determined by hemoglobin A1c (HbA1c) levels] and mortality, graft failure, or DGF was examined [32]. HbA1c (%) was measured quarterly or semiannually for each patient. The patient's average values were assigned to one of seven categories separated by 1% increments: <5%, 5%−6%, 6%− <7% (reference), 7%− <8%, 8%− <9%, 9%−10%, and ≥10%. An HbA1c ≥ 8% was associated with significantly higher all-cause and CV mortality as compared with an HbA1c of 6%− <7% (reference). The HR (and 95% CI) for these adverse events for HbA1c categories of 7%− <8%, 8 to <9%, 9%−10%, and ≥10% were, respectively, 0.89 (0.59−1.36), 2.06 (1.31−3.24), 1.41 (0.73−2.74), and 3.43 (1.56−7.56). Pretransplant HbA1c levels were not predictive of posttransplant graft failure or DGF. It was speculated the elevated blood glucose levels before kidney transplantation may have caused a higher rate of posttransplant infections, inflammation, and other complications of diabetes. It is possible that pretransplant hyperglycemia may be a strong predictor of posttransplant hyperglycemia.

Nutrition screening for transplant candidates

Guidelines regarding nutritional criteria for selection of transplant candidates have mainly focused on obesity and BMI "cutoff" recommendations. While the recommendations for maximal allowable BMI vary, for example, $\mathrm{BMI} \geq 30\ \mathrm{kg/m^2}$ [33,34], $\mathrm{BMI} \geq 40\ \mathrm{kg/m^2}$ [35], most authorities agree obesity per se should not preclude a patient from being considered for kidney transplantation. Often an intervention is recommended to cause weight loss to attain a lower BMI. Some guidelines also recommend screening for other related metabolic abnormalities, for example, CV risk and diabetes.

Current evidence indicates that there are strong associations between abnormal nutritional factors, such as body weight (BMI), change of body weight, body composition, optimal glycemic control, PEW or MIA syndrome, and poor short- or long-term posttransplantation outcomes. However, apart from obesity, the current guidelines have not addressed other nutritional characteristics as part of the screening process. In addition to obesity and BMI recommendations, the recent Kidney Disease: Improving Global Outcomes (KDIGO) guidelines include screening for other nutritional matters, which also tend to be obesity- or weight-related, for example, WHR or undernutrition and frailty, and are largely concerned with their relationship to the transplant patient's postoperative management and healing [36].

Nutritional management of transplant candidates

The majority of kidney transplant candidates are in a maintenance dialysis program, with uncertain waiting times for transplantation that vary from months to years. The long-term exposures of these patients to nutritional derangements caused by uremia, the dialysis procedures per se, comorbidities, physical inactivity and deconditioning [37], are likely to predispose them to poor posttransplant outcomes. Recent reviews [37] and various clinical guidelines [5,38] have described various aspects of nutritional management for maintenance dialysis patients to improve outcomes, such as treating PEW, improving nutritional status and body composition, weight reduction in obese patients, or serum phosphorous control to manage mineral bone disorders (see also Chapter 23: Calcium, Phosphate, PTH, Vitamin D and FGF-23 in CKD-Mineral and Bone Disorder; Chapter 24: Phosphate Metabolism and Fibroblast Growth Factor 23 in Chronic Kidney Disease; Chapter 31: Nutritional Management of Maintenance Hemodialysis Patients; Chapter 32: Nutritional Management of Chronic Peritoneal Dialysis Patients; and Chapter 34: Nutritional Management of the Child with Kidney Disease).

Multifaceted and multidisciplinary management of weight reduction for obese transplant candidates [39] may include dietary counseling and behavioral modification, including the use of a very low calorie diet with meal replacement [40,41], exercise training, pharmacological intervention or bariatric surgery (see Chapters 40–42) [42,43]. Bariatric surgery is known to improve glycemic control or "cure" diabetes in many non-CKD patients [44] and may potentially benefit patients on transplant waitlists. While bariatric surgery appears successful in helping patients move onto transplant waitlists, the long-term safety of losing weight pretransplant is uncertain [45]. All such weight loss treatments should be accompanied by structured dietetic monitoring. Interventions that cause severe deficits of energy or nutrients may induce short- or long-term nutritional complications, for example, anemia, osteoporosis, or protein malnutrition [46], and may paradoxically increase the risk of posttransplant mortality. Exercise intervention by itself may or may not induce weight loss, but it will often engender physical and metabolic improvement [47], both of which are beneficial to patients with ESKD (see Chapter 51: Exercise Training for Individuals With Advanced Chronic Kidney Disease). In summary, nonsurgical interventions should be encouraged as first-line therapy for kidney transplant candidates, despite the current lack of high-level evidence of their value. The exact indications for bariatric surgery for kidney transplant candidates still need to be established.

Nutritional considerations for kidney transplant recipients

What the guidelines say

The posttransplant period is broadly divided into three phases: acute, maintenance, and failing transplant, with the last phase often involved with preparing the patient to return to chronic dialysis. Nutritional challenges change over the life of the kidney transplant patient (Fig. 33.1). Some clinical practice guidelines, such as the CARI [4] and KDOQI [5], provide comprehensive recommendations for nutritional management posttransplantation, whereas the Renal Association guidelines include dietary intervention as part of lifestyle management [48]. KDIGO [49] and the European Renal Best Practice Guidelines [50] mainly focus on the management of obesity and diabetes, including new-onset diabetes after transplantation (NODAT).

As noted earlier, the chapter on transplant nutrition in the third edition of this book [3] was based on the CARI guidelines [4], which were developed through a rigorous consultation process with professionals from various health-care disciplines who care for KTRs [51]. A total of 13 topics were identified for systematic review of the literature; then the evidence was graded and synthesized to formulate evidence-based recommendations. Precisely, 9 of the 13 topics became the CARI guidelines, and the 4 additional topics on nutritional assessment and medications were listed in the Dietitians Association of Australia nutritional guidelines for adult KTRs [52]. This section will now review and summarize the latest nutritional recommendations on the nine CARI guideline topics, including recommendations from such other evidence-based guidelines as the KDOQI, KDIGO, European and Renal Association (UK) guidelines. We will discuss what is known and what has emerged since the previous guidelines and book chapter were published, with a summary of the latest recommendations.

Anemia

Anemia is defined as a hemoglobin (Hb) concentration of ≤ 12 g/dL in women and ≤ 13 g/dL in men. Posttransplantation anemia (PTA) is common both in the early and late posttransplantation periods and is an independent risk factor for CV death, graft failure, and all-cause mortality. PTA is not simply a reflection of low glomerular filtration rate (GFR). Chadban et al. compared a cohort of KTRs with a cohort of community-based people with CKD matched for kidney function and found a 10-fold excess of anemia among the transplant group, a prevalence of 30% versus 3.4% [53]. In another cohort of 1139 KTRs, 36.2% had PTA and 11.7% had severe anemia (Hb $<$ 11 g/dL) [54]. Severe anemia was associated with a reduced composite of patient survival and graft survival during the initial period of time after transplantation ($<$1251 days after transplantation: HR, 6.26; 95% CI, 3.74–10.5; $P < .001$). This study also examined the effect of nutritional deficiencies, such as for iron, folic acid and vitamin B_{12}, on outcomes. A nonsignificant trend for the association between anemia due to nutritional deficiencies (29.1%) and outcome was observed (HR, 3.07; 95% CI, 0.93–10.17; $P = .067$). The relationship to anemia of nutrition-related factors, such as vitamin B_6, protein intake protein-energy status, and presence of PEW, was not examined. Anemia due to acute kidney injury, AR, or infection was also associated with poor outcomes in this early period. Anemia remains highly prevalent and often requires pharmacological treatment with erythropoietin and transfusions. The most identifiable risk factors for PTA are mainly related to clinical morbidity, for example, reduced kidney function, AR, and infection [55].

The majority of guidelines mainly focus on pharmacological management or the use of pharmacological doses of nutrients, for example, iron [56], to manage anemia. There are few or no dietary or nutritional recommendations. Consistent with these guidelines and until more evidence-based data are available, the following recommendations from CARI guidelines on the nutritional management of anemia [57] remain valid:

- No recommendations possible based on Level I or II evidence.

Based on Level III and IV evidence, the suggestion for nutritional care is as follows:

- It is appropriate to use pharmacological doses of nutrients in conjunction with dietary interventions to correct anemia.

Bone disease

Metabolic bone disease is highly prevalent among patients with ESKD. Immunosuppressive therapy, particularly glucocorticoids, and preexisting hyperparathyroidism may further exacerbate the maladaptive responses of bone-mineral metabolism posttransplant. There exists a complex interrelationship between minerals (calcium, phosphorus), vitamin D, bone-related hormones [parathyroid hormone and fibroblast growth factor-23 (FGF-23)] [58] and other relevant nutritional conditions, including low body weight, undernutrition, immobility, and diabetes mellitus, and these factors contribute to the pathogenesis of bone mineral disorders after transplantation, which include renal osteodystrophy, osteopenia, osteoporosis, and osteonecrosis (see Chapter 23: Calcium, Phosphate, PTH, Vitamin D and FGF-23 in CKD-Mineral and Bone Disorder; Chapter 24: Phosphate Metabolism and Fibroblast Growth Factor 23 in Chronic Kidney Disease; and Chapter 25: Vitamin D in Kidney Disease). As a result, KTRs are at high risk of bone fractures and vascular calcification.

Currently, most interventional studies and systematic reviews [58,59] address the use of pharmacological doses of calcium, vitamin D or vitamin D analogs with or without calcium, or bisphosphonates. The role of diet per se in preventing and managing bone disease in adult KTRs is often ignored. The majority of clinical practice guidelines on bone disease in KTRs focus on pharmacological management, including the use of pharmacological doses of nutrients [49,60]. Few if any, of these guidelines make dietary recommendations. Therefore the following recommendations from the CARI guidelines on the nutritional management of bone disease for KTRs [61] are still valid:

- Kidney transplant recipients should be advised to take the vitamin D analog, calcitriol (or another analog) supplement at a dose usually of 0.25−0.50 μg daily. (Level I and II evidence).

Based on Level III and IV evidence, suggestions for nutritional care are as follows:

- A diet containing adequate calcium-rich foods to meet the National Health and Medical Research Council (NHMRC)-recommended daily intake (RDI) for calcium (1000−1300 mg/day) [62].
- The diet should meet the levels of adequate intake for dietary vitamin D that are recommended for the general population, which assume minimal or no Sun exposure [63] to prevent the development of skin cancer.

Diabetes mellitus

Posttransplant diabetes mellitus (PTDM) encompasses the 10%−30% of KTRs with preexisting diabetes and the additional 10%−40% who develop NODAT. PTDM is associated with increased risks of CV disease and mortality, and, to a lesser extent, graft failure [64]. In a cohort of 1146 adult KTRs, 29.8% of patients experienced impaired fasting hyperglycemia, and 13.4% developed NODAT one year after transplantation [65]. A higher risk of developing NODAT was seen in patients who were older, male, had a higher BMI, higher pretransplantation serum glucose and triglyceride levels, and lower serum high-density lipoprotein level. Hyperglycemia was independently associated with all major CV events, including cardiac, vascular, and stroke (HR, 1.11; 95% CI, 1.11−1.13; $P < .0001$; HR, 1.17, 95% CI, 1.14−1.12; $P < .0001$; and HR, 1.16; 95% CI, 1.12−1.19; $P = .003$, respectively). This risk is independent of the presence of CV disease identified before transplantation. A review of randomized controlled trials (RCTs) of diet and/or exercise to achieve weight reduction demonstrated a reduced risk of developing diabetes in the nonrenal populations [66]. Therefore it is reasonable to recommend such interventions to KTRs, with reduced energy diets, moderate-intensity physical activity, and weight control to prevent the development of NODAT. In light of the diabetogenic properties of some immunosuppressive medications and other transplant-related nutritional abnormalities, for example, wound healing and recovery in the acute posttransplantation phase, bone mineral disorders, and PEW, well-designed prospective intervention studies, considering all these nutritional factors might provide helpful insights into methods for preventing NODAT.

The majority of guidelines mainly focus on pharmacological management of NODAT or diabetes to achieve normoglycemia, for example, "Consider targeting HbA1c 7.0%−7.5%, and avoid targeting HbA1c 6.0%, especially if hypoglycaemic reactions are common" [49] (KDIGO guidelines, Section 15.2.2) and "Post-transplant diabetes should be managed in collaboration with specialists in diabetic medicine" [48] (UK Renal Association guideline 6.3). There are no published studies examining the safety and efficacy of dietary interventions for the prevention and management of diabetes in adult KTRs. Therefore the following recommendation from CARI guidelines on the nutritional management of diabetes mellitus [67] remains valid:

- No recommendations possible based on Level I or II evidence.

Based on Level III and IV evidence, suggestions for nutritional care should be as follows:

- In line with guidelines for the management of type 2 diabetes in the general population.

Dyslipidemia

Dyslipidemia is common after renal transplantation and occurs in approximately 60% of patients, both early and late in the course of transplantation. Dyslipidemia is positively associated with kidney graft loss, atherosclerotic CV disease, and CV death [68,69]. According to the Adult Treatment Panel III [70] and the KDOQI working group on managing dyslipidemia in CKD patients [71], dyslipidemia is defined as the presence of at least one of the following serum concentrations: total cholesterol ≥ 200 mg/dL; low-density lipoprotein (LDL) cholesterol ≥ 130 mg/dL; high-density lipoprotein cholesterol ≤ 40 mg/dL; or triglycerides ≥ 150 mg/dL. Posttransplantation dyslipidemia is not synonymous with nonimmunosuppressant-mediated hyperlipidemia, as seen in other clinical conditions [72]. Other potential causes of posttransplant dyslipidemia are genetic predisposition, higher age, excess intake of carbohydrates or saturated fats, obesity, proteinuria, renal insufficiency, and certain antihypertensive medicines, for example, diuretics, beta-blockers. A number of small randomized interventional studies in KTRs with dyslipidemia have shown the safety and efficacy of lipid-lowering with a Mediterranean diet [73,74] or the American Heart Association Step One Diet [75]. Similar effects were found in a number uncontrolled intervention studies [76,77].

The majority of guidelines focus on pharmacological treatment for lipid-lowering or comprehensive treatment algorithms with lifestyle management, including some generic nutritional recommendations, for example, healthy eating (less sugar, cholesterol, and saturated fats in the diet), maintaining a healthy body weight and increasing physical activity or exercise [48,50,78]. The new KDOQI guidelines recommend for kidney transplant recipients a healthy dietary pattern: a Mediterranean diet and increased fruit and vegetable intake [5]. CARI guidelines provided more in-depth recommendations based on Level III and IV evidence (see next). Therefore the following recommendation from CARI guidelines on the nutritional management of dyslipidemia is still valid:

- No recommendations possible based on Level I or II evidence.

Based on Level III and IV evidence, suggestions for nutritional care are as follows *(summary)*:

- To eat a diet rich in whole grain, low glycemic index, and high-fiber carbohydrates, as well as rich sources of vitamin E and monounsaturated fat.
- To eat a diet in line with lipid management guidelines for the general population, a daily fiber intake of 25 g for females and 30 g for males.
- Weight reduction in overweight or obese KTRs.
- Plant sterols and stanols: include plant foods that are naturally rich in phytosterols as well as 2- to 3-g phytosterol-enriched food products (such as margarine, breakfast cereal, low-fat yoghurt or milk enriched with phytosterols).
- Limit alcohol to no more than two standard drinks on any day for both men and women.

Food safety

Immunosuppressive and antibacterial drugs are required lifelong by KTRs to maintain their kidney function. This can increase the risk of food-borne illness from bacteria, viruses, fungi, and parasites [79]. Food-borne illnesses, such as listeria, may impose a serious infection risk for a person who is immunocompromised. Diabetes mellitus, cytomegalovirus infection, and high-dose steroids were identified to be independent risk factors for listeriosis [80]. In an observational study of 102 cases of listeriosis in KTRs, the manifestations of the infection included meningitis, bacteremia, and pneumonia, with a reported mortality rate of 26% [81]. While the incidence of food-borne illnesses may appear low, the effects can be devastating. A comprehensive review on food safety for solid organ transplant (SOT) patients describes the mechanisms, clinical consequences, sources of food-borne illnesses, and food safety practices needed to minimize risks [79]. Prevention is the key, starting with "clean" (handwashing), "separate" (prevent cross-contamination), "cook/chill" (correct time/temperature), and "adequately cook" all animal foods, as well as ensuring safe drinking water. An education program for the patients and their families that involves a dietitian is recommended.

The recommendation from CARI guidelines on the nutritional management of food safety is as follows:

- No recommendations possible based on Level I or II evidence.

Further, there is no Level III or Level IV evidence relevant to food safety. The suggestions for clinical care are based on the available data regarding the incidence and prevalence of food-borne illnesses in this group of patients (summary):

- It is prudent to provide general food safety advice to KTRs.
- A consultation with a dietician is important to identify the most important food safety issues, and
- Dietary modifications relevant to each individual patient, and to ensure dietary requirements are met while food safety precautions are followed.
- The patient should understand that during the early posttransplant period and in periods of acute illness, the likelihood of food-borne infection is high due to significant suppression of the immune system.

Transplant patients are generally motivated by their desire to maintain wellness and personal health and will usually maintain good food safety and hygiene practice in response to credible education information [82]. However, a study examining reported food safety behavior in SOT patients (total = 197, KTRs = 117) found patients often consumed foods that increased their risk of food-borne infections [83]. Within the first year after transplantation, patients reported they followed food safety recommendations rather closely. Although approximately 70% reported they showed concern and sought information on food safety, only 27% recognized all risks of food-borne infection. The incidence of proven food-borne infections was 17.9% 5 years after transplantation (95% CI, 9.9%–30.9%). Most importantly, food-borne infections occurred exclusively among the patients not following food safety recommendations. These results underscore the importance for long-term, ongoing food safety education.

Hypertension

The prevalence of HT among KTRs ranges between 50% and 80%; it is a risk factor for chronic allograft injury, shortened graft survival, and CV morbidity and mortality [84–86]. The risk factors for posttransplant

HT include organ donor age, allograft dysfunction (rejection, DGF, CAN), renal artery stenosis, retained native kidneys, use of calcineurin inhibitors and glucocorticoids, and recipient characteristics, including male gender, age, presence of diabetes, presence of secondary hyperparathyroidism, excess weight gain, pretransplant HT, and high BMI [87–89]. The blood pressure (BP) target is <130/80 mmHg for adult KTRs, and pharmacological interventions are recommended by most guidelines if this BP level is exceeded [49].

Studies to manage HT in KTRs have focused on pharmacological interventions [89,90]. The use of angiotensin-converting enzyme inhibitors or angiotensin receptor blocker inhibitors, and/or calcium channel blockers has been associated with better BP control, longer graft survival, and specific benefits in patients with diabetes and/or albuminuria [90]. Few studies have examined the effect of dietary intervention on BP lowering, and they consist of a number of small RCTs and uncontrolled interventional studies focusing on traditional nutritional factors that are known to be effective in the general population, such as sodium reduction and other special diets. The role of nutritional status and nutrient intake in the pathogenesis and treatment of HT is discussed in Chapter 37, Nutrition and Blood Pressure.

The effectiveness of sodium restriction to lower BP in the general [91,92] and the nondialyzed CKD [93,94] population has been well studied. A dietitian supervised regimen of a no added salt diet providing 80- to 100-mmol sodium/day with antihypertensive medications in one randomized clinical trial [95] and in one uncontrolled trial [96] both led to a significant lowering of BP.

Elevated serum homocysteine (tHcy) is associated with cardiovascular disease (CVD) risk in ESKD and is common among KTRs (see Chapter 26: Vitamin Metabolism and Requirements in Chronic Kidney Disease and Kidney Failure and Chapter 37: Nutrition and Blood Pressure). The Folic Acid for Vascular Outcome Reduction In Transplantation (FAVORIT) trial was a multicenter double-blind RCT to examine the effects of high versus low doses of B vitamin supplements on lowering serum tHcy levels and reducing a composite of incident or recurrent CVD outcomes [97]. Mean follow-up was 4 years with a sample size of 4110 stable KTRs; the amounts of daily intakes of the high versus low doses of the vitamin supplements were, respectively, folic acid (5 vs 0 mg), pyridoxine HCl (vitamin B_6) (50 vs 1.4 mg), and vitamin B_{12} (1000 vs 2 μg). The multivitamin supplements significantly lowered serum tHcy by −4.6 ± 4.5 SD μmmol/L with the high dose vs −0.2 ± 5.1 SD μmmol/L with the low dose (high vs low dose: $P < .0001$). However, the high-dose supplements did not reduce the composite CVD outcome, all-cause mortality, or allograft failure [98]. According to the latest published reports, there are no direct analyses of the effect of vitamin supplements on BP in KTRs [99,100]. In post hoc analyses the results of the FAVORIT trial supported the reduced mortality benefits of lower blood systolic pressure [99] but found no evidence of a BP threshold effect on the risk of allograft failure or estimated GFR (eGFR) decline [100]. Such confounders as diet and lifestyle factors were not monitored in this trial.

In the nonrenal populations the landmark-controlled feeding studies—the Dietary Approaches to Stop Hypertension (DASH) diet [101] and DASH low-sodium diet [92]—lower BP in the absence of weight loss (see Chapter 37: Nutrition and Blood Pressure). The DASH diet is low in saturated fat (≤7%) and total fat, rich in plant-based foods consisting of wholegrain, nuts, fruit, and vegetables and in low-fat dairy products. The DASH diet provides a healthy eating pattern that is rich in nutrients and food components that are beneficial to CV health, for example, potassium, magnesium, calcium, mono- and polyunsaturated fats, vitamin E, dietary fiber, and antioxidants. The DASH low-sodium diet is the same diet but also low in sodium.

At present, there are no controlled interventional studies that examine BP-lowering effects of the DASH diet in KTRs. In a prospective observational study of 632 adult KTRs, baseline dietary data and adherence to the DASH diet were assessed. A validated 177-item food frequency questionnaire was used to calculate the similarity of the participant's usual diet to the actual DASH diet, as indicated by an overall DASH score [102]. After a mean follow-up of 5.3 years, subjects with the highest tertile of DASH score, when compared to the lowest tertile, had a lower risk of both renal function decline (HR, 0.57; 95% CI, 0.33–0.96; $P = .03$) and all-cause mortality (HR, 0.52; 95% CI, 0.32–0.83; $P = .006$). The independent modifiers of the association between the DASH score and these primary endpoints were baseline eGFR and smoking, but not systolic BP. While a significant inverse relationship between the DASH score and BP at baseline was observed in cross-sectional analyses, the ongoing effect of the DASH score on BP alone and outcomes was not known.

The effect of several other nutritional factors on BP in KTRs has also been studied. In a small RCT, all subjects in both study and control groups were encouraged to follow a sodium chloride restricted diet of <3, 6 g/day of fish oil lowered BP significantly more than a control diet providing with 6 g/day of coconut oil [103]. By the end of the study, the low salt, 6 g/day fish oil KTR group required significantly less antihypertensive medication and had significantly higher glomerular filtration rates and effective renal plasma flows and fewer AR reactions. In a randomized crossover study of KTRs and maintenance dialysis (hemodialysis and peritoneal dialysis) patients, twice-daily doses of 4.5-g L-arginine (9.0 g/day), a precursor of nitric oxide (NO), led to a vasodilatory response and lower BP in both KTRs and dialysis [104]. When the supplementation was ceased, both systolic and diastolic BP increased significantly. However, confounders such as dietary and lifestyle factors were not monitored in these two studies.

In summary, there have been no large-scale studies that have established whether nutritional intervention will prevent, control, or mitigate HT in KTRs. The majority of guidelines focus on pharmacological management of HT. Therefore the following recommendation from CARI guidelines on the nutritional management of HT [105] remains valid:

- No recommendations possible based on Level I or II evidence.

Based on Level III and IV evidence, suggestions for nutritional care are as follows *(summary)*:

- Stable hypertensive kidney transplant recipients should be advised to restrict sodium intake to 80–100 mmol/day (Level III evidence).
- Based on studies in the general population kidney transplant recipients should, when overweight or obese, be encouraged and supported to reduce their weight and be encouraged to do at least 30 min of moderate-intensity physical activity on at least 5 days per week.
- Alcohol should be limited to no more than two standard drinks on any day for both men and women. This advice is based on NHMRC guidelines for lifetime health risks associated with daily alcohol consumption by “healthy” men and women [106].

Based on the evidence from the general population and people with mild to moderate CKD, as described in Chapter 37, Nutrition and Blood Pressure, it seems prudent to also advise KTRs to follow the DASH low-sodium and Mediterranean diets, but perhaps with lower dietary protein intakes (~0.8 g protein/kg/day).

Hypophosphatemia

Hypophosphatemia, defined as a serum phosphorus level <0.8 mmol/L (<2.5 mg/dL), is common in KTRs. It affects 40%–90% of KTRs during the first months after transplant and may persist for up to 10 years in 25%–30% of recipients [107]. There are two major mechanisms for the hypophosphatemia: (1) reduced intestinal phosphate absorption and (2) high urinary phosphate loss caused by hyperparathyroidism and elevated serum FGF-23, immunosuppressants for example, high doses of steroids and tacrolimus and tubular damage [108–111]. Hypophosphatemia can cause muscle weakness; in the general population, acute cases of severe hypophosphatemia can cause seizures, rhabdomyolysis, respiratory failure, hemolysis, and myocardial depression [112]. In the long term, it may increase osteodystrophy and fracture risk in KTRs [110]. The abovementioned effects are seldom described in the KTR literature [113,114], except in rare cases of acute phosphate nephropathy leading to impaired allograft function [115,116]. Despite such potential detrimental effects, posttransplant hypophosphatemia is associated with better graft and patient survival [117].

The following recommendations from the CARI guidelines on the nutritional management of hypophosphatemia [118] remain applicable:

- No recommendations possible based on Level I or II evidence.

Based on Level III and IV evidence, suggestions for nutritional care are as follows *(summary)*:

- Physicians should be aware that phosphate supplementation has the potential to worsen hyperparathyroidism and may mask phosphorus deficiency beyond 3 months posttransplant (Level IV evidence).
- Kidney transplant recipients should be advised to consume phosphate-rich foods as early as possible after transplantation, once good graft function is achieved.
- Supplementation may be considered if hypophosphataemia persists despite an adequate dietary phosphate intake. The serum phosphate level at which supplementation may be considered and the dose of replacement to be given is unclear and clinical judgment is required.

Overweight and obesity

The presence of, and degree of, overweight and obesity at the time of transplant are associated with increased risk of surgical and wound complications, but not inferior graft and patient survival, as discussed earlier and in a systematic review [119]. After a successful kidney transplant, several factors tend to promote weight gain resulting in overweight (BMI, 25–29.9 kg/m^2) or obesity (BMI ≥ 30 kg/m^2). There is relief of uremia improving appetite, removal of the dietary restrictions integral to chronic dialysis treatment, the appetite-enhancing effects of corticosteroid use, and, for many KTRs, continuation of a very sedentary lifestyle. Hence, transplant weight gain and KTRs often gain an amount of body weight equivalent to 10%−35% of their pregain weight. Weight gain mostly occurs during the first year posttransplant [12,120], with women more prone than men to become obese [121] and higher weight gains seen in indigenous populations [122]. Weight gain is often associated with an increase in fat mass rather than muscle mass [123]. For patients who are undernourished pretransplant, some weight gain may be desirable, but undesirable or excess weight gains are associated with poor short- and long-term outcomes [13]. In one cohort study the greatest survival was associated with 10%−19.9% weight gain in the first year and stable weight (0%−4.9% gain) in the second year. Conversely, a weight gain of 20% or greater during the first year and a 10% or greater weight gain in the second year was associated with increased death risk (year 1: HR, 1.78; 95% CI, 1.13−2.81, $P = .013$; year 2: HR, 1.67; 95% CI 1.01−2.76; $P = .047$). Causes of death were CVD, cancer, infections, and other factors. Weight gain 6 months after transplantation resulting in obesity was independently associated with a statistically significant increase in the incidence of posttransplant HT, diabetes mellitus, and ischemic heart disease [124].

A number of interventional studies show improvements in body weight and other health outcomes in overweight and obese KTRs. In a 2-year RCT a structured dietetics intervention with a Mediterranean-style diet resulted in healthier eating habits and a "trend" for weight loss [125]. In this study the mean transplant vintage was approximately 4.3 years at enrollment, and nutritional intervention failed to achieve significant weight loss in these KTRs. Early intervention to prevent undesirable weight gain may be a more effective measure. In a small, nonrandomized prospective interventional trial, the study group had significantly lower mean weight gain than historical controls, who had not received nutritional advice, at 4 months (1.4 vs 7.1 kg; $P = .01$) and at 1 year (5.5 vs 11.8 kg; $P = .01$). These results support early intensive dietary advice and follow-up to control weight gain during the first year posttransplantation [126].

The "**Inten**sive **N**utrition intervention vs standard nutrition care to avoid excess weight gain after kidney **T**ransplantation" (The INTENT Trial) was an RCT designed to examine the ability of an intensive nutrition and exercise intervention to reduce weight gain 1 year posttransplantation [127]. Counseling sessions were provided by a renal dietitian on four occasions to the standard care group ($n = 18$) and on 12 occasions to the intensive intervention group ($n = 19$). The intensive intervention group also received an exercise plan from an exercise physiologist delivered over three visits. The primary outcome measure was weight, and secondary outcomes were body composition, biochemistry, physical function, and quality of life. Both the standard and intervention groups had a moderate and similar increase in weight at 1 year 2.5 ± 4.0 SD kg versus 4.9 ± 5.9 kg, respectively (difference between the two groups; $P =$ NS.), and between-group differences in the secondary outcomes were not observed. However, across the entire cohort, all secondary outcomes improved, except for total body fat, fasting blood glucose and HbA1c [128]. The authors concluded that KTRs did not benefit from an intensive nutrition intervention compared with standard care, although study participants did not gain as much weight as expected—as noted earlier, weight gain during the first year posttransplant is commonly >10%. The lack of an observed difference may have been due to the "Hawthorne effect," where studied subjects alter their behavior due to their awareness of being observed. A personal communication with the authors of this study indicated all participants attended the same transplant clinic and shared information, increasing the probability of this explanation. An alternate explanation may be the effectiveness of the "standard care" received in this trial—four dietitian interventions per year. Similarly good outcomes with regard to weight and other parameters, for example, body composition, serum lipid profile, and BP, were observed in an uncontrolled intervention trial in which dietitians provided diet prescription with about four to five consults during the first year [129]. However, structured nutrition intervention is frequently not available to KTRs, and best practice guideline recommendations are commonly not met due to inadequate dietitian services [130,131]. Many units only practice selective referral for ad hoc interventions for weight reduction after excess weight gain.

In recent years, more attention has been focused on bariatric surgery for weight loss in obese kidney transplant candidates or KTRs (see also Chapter 41: Bariatric Surgery and Kidney Disease). In one study [132] a cohort of 43 obese pretransplant patients had a median BMI of 43 (IQR 38−48) kg/m^2 at the time of their bariatric surgery. At the time of kidney transplantation, their median BMI had decreased to 32 (IQR 28−36) kg/m^2. In the first 5 years (43 months, IQR 20−89) after the transplantation, their median BMI was 33 kg/m^2. This reflected a sustained loss of 22% of their body weight. The authors also compared the effects of bariatric surgery performed before and after transplantation, it resulted in a similar maintenance of weight loss (36 vs 32 kg/m^2, $P = .814$) 5 years after kidney transplantation. Compared with matched controls from the national registry, the effect of bariatric surgery on kidney transplantation was associated with a decreased risk of allograft failure (HR, 0.85; 95% CI, 0.85–0.86; $P < .001$) and mortality (HR, 0.80; 95% CI, 0.79–0.82; $P < .001$). In this study, bariatric surgery before or after transplantation appeared to be a safe and effective approach to weight loss, and improved long-term allograft and patient survival, although other nutritional characteristics of the patients were not noted.

In summary the literature provides only limited evidence to support the beneficial effects and the optimal methods of nutritional intervention to either prevent weight gain or reverse obesity in KTRs. The available data suggest a multifaceted approach to prevent and manage obesity, which includes tailoring immunosuppressants, early structured dietitian intervention, engaging in healthy eating and exercise, and, when indicated, bariatric surgery.

Transplant guidelines note the importance of monitoring obesity [49]. The 2010 CARI guidelines on the nutritional management of overweight and obesity in adult KTRs [133] state the following:

- No recommendations possible based on Level I or II evidence.

The results of the INTENT trial did not add any high level of evidence. Based on Level III and IV evidence, suggestions for nutritional care are as follows *(summary and selective information)*:

To prevent excessive weight gain (Level III):

- Kidney transplant recipients should be referred to a dietitian as soon as practicable after transplantation, for written and verbal advice for preventing weight gain.
- Regular follow-up should be arranged to prevent excessive weight gain.

To reduce body weight in overweight or obese kidney transplant recipients (Level IV):

- A diet that is individually planned with a moderate energy restriction of about 30% of energy expenditure should be applied.
- Overweight and obese kidney transplant recipients are more likely to make dietary changes and lose weight with monthly follow-up with a dietitian.

Dietary protein requirements

The CARI guidelines on protein requirements for KTRs have been widely adopted in clinical practice and intervention studies since they were published in 2010 [134], but, since then, there have been limited metabolic studies on protein and energy requirements for this population. Posttransplant nutritional considerations can be broadly divided into two periods, the acute and maintenance phases, with the maintenance phase further divided into before and during a later phase of a failing transplant kidney (Fig. 33.1). During the acute posttransplant phase, which comprises the first 4–6 weeks posttransplantation, high doses of immunosuppressants, surgical stress, and wound healing increase the demand for nutrients. Unmet needs may lead to negative nitrogen balance, increased catabolism, and decreased anabolism of body protein that may result in delayed wound healing, loss of muscle mass, and a compromised immune system. A high-protein (~1.4 g/kg per day), high-energy (~35 kcal/kg per day) diet in KTRs is required to maintain neutral or positive nitrogen balance and to limit Cushingoid side effects. Individualized energy prescription is required in the presence of malnutrition, obesity, inflammation, or other adverse events such as sepsis or infection.

KTRs enter the maintenance phase after graft function has stabilized and immunosuppressive medications have been adjusted to maintenance doses. However, optimal levels of protein and energy intake to preserve long-term graft function have yet to be established. To maintain normal nutritional status the current recommendation for optimal protein intake is near the RDI levels (0.75-g protein/kg body weight for females and 0.84-g protein/kg body weight for males) and energy intake is consistent with dietary guidelines for healthy adults (25–35 kcal/kg IBW/d), based on age, gender, level of physical activity, body composition, weight status goals, and concurrent illness or presence of inflammation. These recommendations are also similar to the recommended dietary energy intake for nondialyzed CKD patients [135].

The following recommendation from CARI guidelines on dietary protein requirements [134] remains valid:

- No recommendations possible based on Level I or II evidence.

Suggestions are based on Level III and IV evidence *(summary)* are as follows:

- In the first 4 weeks after transplant a diet providing at least 1.4-g protein/kg body weight may reverse negative nitrogen balance and lead to increased muscle mass in kidney transplant recipients (Level III).
- There is currently no evidence available regarding the long-term protein requirements of stable kidney transplant recipients. Stable kidney transplant recipients on a maintenance immunosuppression regimen, irrespective of renal function, should not exceed the NHMRC Australian Government—RDI of

protein for the general population—0.75 g protein/kg body weight for females and 0.84 g protein/kg body weight for males.

- Regular review by a dietitian is desirable in the long term to ensure that protein requirements are neither exceeded (potentially placing unnecessary pressure on the kidney graft) nor inadequate (possible in periods of AR when prednisone dose may be increased).

Other nutritional issues

Malnutrition

In contrast to common thinking, the dietary freedom and robust appetite due to corticosteroid therapy after kidney transplantation does not always lead to better nutritional status. Suboptimal nutritional status can occur in the acute or maintenance phases after transplantation, especially if the transplanted kidney function decreases to a predialysis stage of CKD (Fig. 33.1). A total of 15%−60% of transplant patients who develop advanced CKD have been found to have malnutrition or PEW [136−138], and a high malnutrition−inflammation score [139]. These conditions predict depressive symptoms [140], anemia [141], and increased risk of mortality [138]. Factors affecting nutritional status of these patients include preexisting undernutrition and comorbidities and treatments that promote increased energy expenditure and requirements and net protein catabolism, such as immunosuppressive medications (e.g., corticosteroids), acute or chronic graft rejection; the uremic syndrome, anorexia, infection, other inflammatory diseases, hospitalizations and hormonal and other metabolic derangements [29,137,142,143].

In summary the prevalence and effects of malnutrition (PEW) in KTRs cannot be underestimated. Therefore sound clinical practice should include careful monitoring of immunosuppressive medications, prevention and treatment of infection and inflammation, and provision of structured nutritional care to prevent or treat malnutrition. Regular nutritional assessment, education, and monitoring are all important practices to improve outcomes.

Summary of recommendations for intake of energy and other nutrients

The energy and nutrient requirements, rationales, and recommendations described earlier and in various clinical practice guidelines [4,135] are summarized in Table 33.1.

Current trends and latest topics of interest

In recent years a "whole food" approach for therapeutic dietary management has gained tremendous recognition. The patient's microbiome and dietary patterns are two most promising topics that may have potential to improve outcomes in nonrenal and CKD patients, and such approaches may complement the nutritional management of kidney transplant patients. These are described next and summarized in Table 33.2.

Gut microbiome

The "microbiome" is a collective term referring to the genetic material within a microbiota, with gut microbiota being "the community of bacteria that reside in the gastrointestinal track." Gut microbiota influence the nutrition, metabolism, physiology, and immune function of the body. The composition of the gut microbiota is affected primarily by diet; however, drugs, including antibiotics and major health events, such as development of diabetes, kidney disease, and transplant surgery, also play a major role [141,142]. Some compounds that accumulate in kidney failure lead to increased production of potential toxins in the gut. Consumption of "synbiotics" (a combination of prebiotics and probiotics) [144] may be used to modify the gut microbita. Prebiotics are components of the diet that are selectively utilized by microorganisms to confer health benefits to the host and include inulin and fructo- and galacto-oligosaccharides. Probiotics are live bacteria that are beneficial to health when administered in adequate amounts. Examples include plain yoghurt, cottage cheese, apple cider vinegar, and fermented foods, for example, kimchi and miso [145].

Important determinants of the composition of gut microbiota in CKD are protein, dietary fiber, synbiotics, and bioactive compounds such as polyphenols. Nutritional interventions to modify these food components may modulate gut microbiota to alleviate gut dysbiosis in CKD and hence clinical outcomes [145,146]. In CKD, gut microbiotia imbalance or dysbiosis is common and is associated with increased protein-bound uremic toxins, for example, p-cresyl sulfate and indoxyl sulfate, inflammation, and oxidative stress, which are in turn associated with CVDs, morbidity, and mortality [145,147]. A recent comprehensive review discussed the role of the gastrointestinal microbiota in posttransplant associated infections and potential therapeutic options [148]. There is limited evidence for the effectiveness of synbiotic supplementation on reducing uremic toxins [149] or other

TABLE 33.1 Energy and other nutritional requirements after kidney transplantation.

Phase, posttransplant	Immediate or acute	Maintenance
Immunosuppressant dose	High	Maintenance
General comments	Pretransplant diet (usually dialysis diet) until graft functions (see next) Higher protein and energy requirements due to stress of surgery and steroids therapy Strict food safety practice	Healthy and balanced eating as per local dietary guidelines for healthy adults and aligned with DASH and Mediterranean diets (see dietary pattern)
Energy (kcal/kg IBW/d)	30–48 Aim to attain and maintain IBW depending on physical activity level	25–35 Adapted to individual needs to attain healthy weight and optimal nutritional status depending on age, gender, and physical activity levels
Protein (g/kg/d)	1.4	0.75–1.0 (RDI)
Sodium	Usually no restriction in patients with a functional graft May need to increase intake during the polyuric phase	Restricted if HT present, 100 mmol/d or <2.3 g/d (no added salt)
Potassium	Usually no restriction in patients with a functional graft May need to increase intake during polyuric phase	No modifications unless serum potassium is elevated
Calcium (mg/d)	1200–1500	RDI or RDA 1000–1300 according to age group
Phosphorus (mg/d)	~1200 May need phosphate supplementations if serum phosphate is low	No modifications unless serum phosphate is elevated OR when renal function re-entering CKD stages 3–5, to adjust dietary phosphorus intake to maintain serum phosphate levels in the normal range
Other vitamins and minerals	Near RDI or RDA levels	Near RDI or RDA levels
Vitamin and mineral supplementation	Individualized supplementation by nephrologist, for example, iron, phosphate	Individualized supplementation by nephrologist if required
Fluid	A high fluid intake may be needed to maintain balance	Normal intakes

CKD, Chronic kidney disease; *DASH*, Dietary Approaches to Stop Hypertension; *HT*, hypertension; *RDA*, recommended daily allowance of respective countries; *RDI*, recommended daily intake.

markers and clinical outcomes in CKD [150,151]. These RCTs have been focused on nondialysis CKD and maintenance dialysis patients [150].

In KTRs, infection and rejection complications might result from a liberalized diet after transplantation, as well as from immunosuppressive medications, altered bowel transit time (e.g., postoperative ileus, constipation), or prophylactic and therapeutic antimicrobial agents introducing a new gut microbiota that alters the gut immunomodulation. Gastrointestinal upsets such as diarrhea and urinary tract infections are common posttransplant infections. Potential nutritional interventions therefore include synbiotics from diet or supplements. To date, interventional studies to explore the effects of changing the microbiome in KTRs have not been undertaken [148,150]. In summary, until the results of good clinical trials are available to inform recommendations, KTRs are encouraged to ingest foods that are high in dietary fiber and that contain prebiotics and probiotics (see Table 33.2).

Dietary patterns

Food and drinks provide energy and nutrients. Food synergy is an important concept that acknowledges the additive effects of dietary constituents on health [152,153]. Dietary patterns describe the overall diet, foods, food groups and nutrients, their combination and variety, and the frequency and quantity with which they are habitually consumed [154,155]. The characteristics and benefits of individual core food groups on the health of CKD patients have been reviewed extensively [156] to support a food-based approach to nutritional intervention. There is little evidence to support individual nutrients working in isolation to exert significant health benefits, for

TABLE 33.2 Recommended food choices for kidney transplant recipients.

		Important food components				**Potential benefits for KTRs**
Food[a]	**Main nutrient**	**Dietary fiber**	**Pre-and probiotics**	**Antioxidants**	**Flavonoid/ isoflavones**	***Deduced from general and CV health, nondialysis CKD studies***
Core food groups						
Bread, cereals and grain products Whole meal/whole grain products	CHO (unrefined), PO_4, VitBs and E	✓	✓	✓		↓ Constipation gut microbiota health *Others:* *↓ CRP levels (E)* *↓Myocardial infarction risk (E)* *Low GI:* *↑Insulin sensitivity (I)* *↓ Mortality (E)*
Fruit *Vegetables* Variety of seasonal colored vegetables *High in prebiotics: starch-resistant* *High in probiotics: fermented vegetables, for example, sauerkraut, kimchi*	Vit A, C, and K Vit A, C, and K, Mg, folate, iron in green leafy veg	✓	✓	✓	✓	Constipation gut microbiota health *Others:* *BP (I)* *CRP (I)* *↓Inflammation and oxidative stress (E)* *Acidosis (I)* *CV and all-cause mortality (E)* *Low GI:* *↑ Insulin sensitivity (I)*
Meat and alternatives Includes eggs, plant-based proteins, for example, dried beans, legumes, nuts, and seeds Lean cuts of meat, skinless poultry, fish; vegetarian proteins (unsalted) *High in probiotics: miso, tempe, fermented soya beans*	Iodine, iron, PO_4, protein, VitBs and B_{12} and zinc Omega-3 fatty acids and VitD (in oily fish) $N-6$ fatty acids and Vit E (in nuts)	Plant-based proteins ✓	Plant-based proteins ✓	Plant-based proteins ✓	Plant-based proteins ✓	Low AGE products—altered gut microbiome, which may reduce CV risk *Others:* *Fatty fish:* *↓ CV and all-cause mortality (E)* *↓Risk MI, ischemic heart disease, stroke (E)* *Plant-based protein:* *↓Serum lipids (I)* *↓ CRP (I)*
Milk/dairy and alternatives Fat-reduced varieties if needing to control weight *High in probiotics: yoghurt*	Calcium, PO_4, protein, Vit B_2, An and D		✓	✓		Limited data in TP Phosphate restoration early after transplant *↑ Muscle and bone density (I)*
Fat Mono- or polyunsaturated fats. Limit saturated fats and trans-fats	Essential fatty acids, fat-soluble vitamins			✓	✓	Limited data in TP *↓ Serum lipids (I)* *↓ Markers of oxidative stress*
Other foods and dietary patterns						
Alcohol Limit: moderate	Alcohol			✓		Limited data in kidney health
Salt/sodium Limit to 80−100 mmol/d, avoid processed and salted foods	Sodium					↓ BP (TP and I)

(*Continued*)

TABLE 33.2 (Continued)

Food[a]	Main nutrient	Important food components				Potential benefits for KTRs
		Dietary fiber	Pre-and probiotics	Antioxidants	Flavonoid/ isoflavones	*Deduced from general and CV health, nondialysis CKD studies*
Sugars Limit, or optimal level for energy	CHO (refined)					– –
Healthy dietary patterns Local dietary guidelines plus DASH and Mediterranean-style diets that emphasize plant-based foods, good quality animal protein, low sugar	From all core food groups	✓	✓	✓	✓	*Limited data in TP* *Others:* ↓*BP (I)* ↑ *Serum albumin (I)* ↓ *Serum lipid (I)* ↓ *Inflammation (I)*

[a] *Quantity depending on age, gender and physical activity levels.*

AGEs, Advanced glycation end products; *BP*, blood pressure; *CHD*, coronary heart disease; *CHO*, carbohydrates; *CKD*, chronic kidney disease; *CRP*, C-reactive protein; *CV*, cardiovascular; *E*, epidemiology study; *EFV*, extracellular fluid volume; *GI*, Glycaemic Index; *I*, intervention study; *IHD*, ischemic heart disease; *IS*, insulin sensitivity; *K*, potassium; *KTRs*, kidney transplant recipients; *Mg*, magnesium; *MI*, myocardial infarction; *Na*, sodium; *PO_4*, phosphorous; *TP*, information from kidney transplant specific study; Vit, vitamin.

example, the FAVORIT trial [98]. The most highly cited studies of the effects of diet patterns on health in the nonrenal population are the DASH [101] and Mediterranean [157] diets, which share many common features [158] (see Chapter 37: Nutrition and Blood Pressure). The Mediterranean diet also emphasizes the inclusion of olive oil. Other important dietary patterns align with dietary guidelines of individual countries, which take into account regional cultural eating patterns; examples are guidelines for people in Australia [159], Nordic countries [160], and United States [161]. These dietary patterns not only provide guidelines for healthy eating to meet nutrient requirements, expressed as RDIs or recommended daily allowances, but also to reduce the risk of cancer and other chronic diseases. Some guidelines are also designed for therapeutic intervention, for example, lowering BP [162], improving blood lipid profiles or increasing insulin sensitivity [163]. The common features of these dietary patterns are high consumption of fruit, vegetables, whole grains, legumes, seeds, nuts, fish and dairy products, and low consumption of meat (especially processed meat), sugar, and alcohol.

A number of epidemiological studies have described associations between a healthy dietary pattern and reduced risk of CKD [164], delaying progression and improving survival in nondialysis CKD stages 4–5 [165], as well as reduced mortality [166]. However, studies of the effects of dietary patterns on the health of KTRs have been limited. As discussed earlier in the *Hypertension* section, adherence to a DASH-style diet is associated with a lower risk of both renal function decline and all-cause mortality [164,167]. In a cohort of 632 KTRs, good adherence to the Mediterranean diet was inversely associated with graft failure (HR, 0.68; 95% CI, 0.50–0.91), kidney function decline (HR, 0.68; 95% CI, 0.55–0.85), and graft loss (HR, 0.74; 95% CI, 0.63–0.88) [168]. The Modification of Diet in Renal Transplantation study [169] is currently underway to examine the effects of a low-fat (<15% energy), unrefined plant-based diet versus the Mediterranean diet (control); the primary outcome measure is serum LDL cholesterol and other secondary measures that are validated risk factors for adverse CV events.

Diet recommendations for the KTRs are frequently inferred from the results of studies in nondialyzed CKD patients, as the maintenance phase of kidney transplantation is often considered to be the "returning to the nondialysis-dependent CKD stage." However, the medications commonly used in the posttransplant phase, and in particular, immunosuppressants and antibiotics, introduce additional physiological and metabolic challenges to nutritional intervention studies. Whether nutritional interventions that are effective for the general and nondialyzed CKD populations are also effective in KTRs remains uncertain and may be difficult to predict in the absence of clinical trials of KTRs. For example, one epidemiological study in hemodialysis patients found no evidence of benefit for Mediterranean or DASH diets with regard to adverse CV events or total mortality [170]. Food-based dietary recommendations for healthy gut microbiota and dietary patterns for KTRs are summarized in Table 33.2.

Conclusion

This chapter summarizes the various aspects of nutritional management and dietary recommendations for KTRs, from the pretransplant stage to the acute and maintenance phases posttransplantation. Over the past decade, there has been an increase in both observational and intervention studies that examine the efficacy and safety of nutritional intervention to improve specific health outcomes for KTRs. However, many questions remain unanswered, and current food-based recommendations and guidelines frequently extrapolate findings from studies in the general population or in CKD patients. The limitations of this approach must be acknowledged, given the complexity of the post-transplantation health environment. Acknowledging these limitations, the authors recommend a combined energy−nutrient prescription that is time-dependent after transplantation as the nutritional needs of KTRs change overtime. Nutrient recommendations should be delivered within the framework of the DASH and Mediterranean-style diets in concert with the local cultural patterns of dietary intake. Ultimately, large-scale RCTs are needed to adequately inform nutritional practice. Until then, evaluation of the implementation of these nutritional guidelines may help to direct and improve clinical practice and patient outcomes.

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CHAPTER

34

Nutritional management of the child with kidney disease

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Protein—energy malnutrition (PEM) is a common problem in children with chronic kidney disease (CKD). While the exact prevalence of PEM in children with CKD is not known, an indirect estimate can be gauged from the prevalence of growth failure in these patients, especially during the first few years of life. While several factors such as metabolic acidosis, calcitriol deficiency, renal osteodystrophy, and most importantly tissue resistance to the actions of growth hormone (GH) and insulin-like growth factor-I (IGF-I) contribute to the impaired skeletal growth of children with CKD, malnutrition plays a critical role. Clinical experience suggests that inadequate nutrition may also contribute to an impaired neurodevelopmental outcome in the youngest patients with renal insufficiency [1—4]. Most importantly, physical manifestations of poor growth, such as short stature and low body mass index (BMI), have been associated with an increased risk of mortality in children with CKD [5].

PEM that occurs because of insufficient nutritional intake or an improper diet results in adaptive responses to a negative energy balance, such as hunger, decreased energy expenditure, and preservation of lean body mass in preference to fat mass. These physiologic responses are usually totally reversed by restoring adequate nutritional intake. However, a maladaptive response to a negative energy balance that is characterized by anorexia, increased energy expenditure, muscle wasting, and relative underutilization of fat is less likely to respond to nutritional support only. This maladaptive response has been termed protein-energy wasting (PEW) and the consensus statement by the International Society of Renal Nutrition and Metabolism defined it as a state of metabolic and nutritional derangement characterized by decreased body stores of protein and fat [6]. The severe degree of PEW, also referred to as cachexia, has been shown to be the strongest predictor of mortality, especially in the adults and the elderly [7].

Until recently, PEW has been understudied and poorly characterized in children with CKD due to challenges associated with the application of adult-defined PEW criteria to the pediatric population. In adults with CKD the diagnosis of PEW is made based on deranged biochemical parameters, reduced body mass, reduced muscle mass, and decreased dietary protein intake (DPI). In children with CKD, these criteria are confounded by abnormal growth and development. Weight loss, which is an essential component of cachexia in adults, is not an appropriate criterion in children who are growing. Therefore a lack of expected weight gain, presenting as a downward shifting of BMI percentiles, is a more reasonable marker to identify growth failure in children. It should be noted that due to the high prevalence of growth retardation and delayed puberty in children with CKD, BMI should be expressed relative to height age (the age at which the child's height would be at the 50th percentile) instead of chronological age. Abraham et al. assessed the prevalence of PEW in a cohort of children with mild-to-moderate CKD in the Chronic Kidney Disease in Children (CKiD) study by using modified pediatric diagnostic criteria, such as a lack of expected weight gain instead of weight loss and BMI for height age. Based on these criteria, the authors reported a PEW prevalence of 7%—20% [8]. Additionally, when

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growth indices such as height standard deviation score (SDS) or height velocity SDS were included in the criteria, the presence of PEW was associated with an increased risk for hospitalization [8]. It is noteworthy, that in patients with PEW, overaggressive nutritional supplementation does not completely reverse the body composition abnormalities, notably muscle wasting, and may lead to relative obesity in patients with cachexia [9]. As a result of its major negative impact on growth, PEW in children with CKD is also termed uremic failure to thrive [10].

While PEM and PEW in children with CKD have been recognized for decades, aggressive nutritional supplementation in these children with nasogastric or gastric tube feeding has also led to an increased prevalence of obesity [11]. Data from the International Pediatric Peritoneal Dialysis Network (IPPN) has revealed that being overweight is emerging as a greater problem than undernutrition among children receiving peritoneal dialysis (PD) in developed countries. The latest report from IPPN reported that the overall prevalence of obesity/overweight was 19.7% in comparison to undernutrition that was 8.9% [12]. While underweight was most prevalent in South and Southeast Asia (20%), Central Europe (16.7%), and Turkey (15.2%), overweight and obesity were most common in the Middle East (40%) and the United States (33%) [12]. In addition, the North American Pediatric Renal Trials and Collaborative Studies (NAPRTCS) database and other reports have shown an increasing prevalence of obesity in pediatric patients with mild CKD, as well as in those awaiting transplantation [13,14]. Multivariate analysis of BMI SDS has shown a U-shaped association between BMI and the risk of death, with extremes in BMI associated with an increased risk of mortality in children with stage 5 CKD [5,15]. Interestingly, this finding contrasts with the data from adults on maintenance dialysis, in whom increased weight seems to be associated with an improved outcome [16].

Thus the therapeutic goals of optimal nutritional therapy of children with CKD should be to maintain BMI as well as linear growth within the normal range and prevent biochemical derangements. The goal of this chapter is, in turn, to provide the reader a comprehensive review of the many factors that impact the nutritional status of infants, children, and adolescents with CKD or receiving maintenance dialysis and to provide treatment recommendations. Since the last publication of this chapter in 2013, the Pediatric Renal Nutrition Taskforce (PRNT) has published clinical practice recommendations (CPRs) on energy and protein requirements [17], and the dietary management of calcium and phosphate [18], in children with CKD stages 2–5 and on dialysis. Where appropriate, information derived from these recent CPRs will be incorporated into this text.

Etiology of malnutrition

The origin of PEM/PEW in children with CKD is multifactorial (Table 34.1); however, an inadequate dietary intake is considered a major contributing factor, especially in infants [19]. Nausea and vomiting are common in infants and children with CKD, with delayed gastric emptying and gastroesophageal reflux being detected in as many as 73% of patients with CKD [20]. Whereas the etiology of these gastrointestinal abnormalities is unclear, factors such as autonomic dysfunction and the actions of uremic toxins on gastric smooth muscle activity have been implicated [21].

TABLE 34.1 Causes of protein–energy malnutrition in children with chronic kidney disease.

- Inadequate food intake secondary to
  - anorexia
  - altered taste sensation
  - nausea/vomiting
  - emotional distress
  - intercurrent illness
  - unpalatable prescribed diets
  - imposed dietary restriction
  - impaired ability to procure food because of socioeconomic situation
- Chronic inflammatory state
- Catabolic response to superimposed illnesses
- Possible accumulation of endogenously formed uremic toxins and/or the ingestion of exogenous toxins
- Removal of nutrients during dialysis procedure
- Endocrine causes such as
  - resistance to the actions of insulin and IGF-I
  - hyperglucagonemia
  - hyperparathyroidism

IGF-I, Insulin-like growth factor-I.

The taste sensation of patients with CKD is frequently altered and likely also influences the voluntary nutrient intake. Although zinc depletion has been linked to anorexia, and a low dietary intake of zinc and low serum zinc concentrations has been reported in children with decreased taste acuity undergoing maintenance dialysis [22,23], a benefit of supplementation with zinc in terms of improving taste acuity and appetite has not been clearly demonstrated. Serum levels of a small peptide hormone "leptin" have been shown to be elevated in patients with CKD and those undergoing maintenance dialysis. Produced mainly in adipose tissue and primarily cleared by the kidney, it is speculated that hyperleptinemia might also contribute to uremic anorexia and malnutrition [24,25]. Finally, patients with CKD usually receive multiple medications, and drugs such as angiotensin-converting enzyme inhibitors or antihistamines may adversely influence taste perception and, in turn, nutrient intake [26,27].

Adolescents are a unique patient group who appear to be particularly vulnerable to malnutrition due to their poor eating habits. They skip meals, favor fast foods, and, in the presence of imposed dietary restrictions associated with advanced CKD, find it difficult to meet the nutritional requirements of normal pubertal growth and development. The diagnosis/presence of advanced CKD may result in substantial emotional distress in many patients and their families, which may adversely affect nutritional intake as well. Finally, the socioeconomic status of the family might also, on occasion, prevent the patient and family from procuring appropriate food items, so-called food insecurity. Historically, household food insecurity has been assessed by indirect methods, such as food availability, purchasing power, consumption profile, and anthropometric measurements, with the main objective to quantify the number of individuals experiencing food shortage or even outright hunger. Several tools have been proposed for measuring the perception and/or experience of families suffering from food insecurity. The Core Food Security Measurement and the Household Food Security Survey Module used by the Food and Nutrition services of the US Department of Agriculture form the basis for most of the currently used instruments to detect food insecurity [28].

In contrast to simple PEM, which is caused by decreased intake alone, PEW is defined as a complex metabolic syndrome associated with an underlying chronic illness and characterized by a loss of muscle, with or without the loss of fat. While inadequate intake may contribute to PEW, recent evidence indicates that other factors such as systemic inflammation, endocrine perturbations, and abnormal neuropeptide signaling play important roles in wasting in the context of CKD. Several review articles provide a comprehensive perspective of PEW in children with CKD [9,10,29].

Assessment of nutritional status

Assessment of the nutritional status of children with CKD requires the evaluation of multiple indices, as there is no single measure that by itself can accurately reflect a patient's nutritional status. A variety of physical measurements and anthropometric data plotted on appropriate growth charts, along with an evaluation of the dietary intake, are required to provide a complete picture. The recommended frequency of the nutritional evaluation depends on both the age of the child and the severity of CKD (Table 34.2).

TABLE 34.2 Recommended parameters and frequency of nutritional assessment for children with chronic kidney disease (CKD) stages 2–5 and 5D [30].

	Minimum interval in months									
	Age 0– <1 year			**Age 1–3 year**			**Age >3 year**			
Measure	CKD 2–3	CKD 4–5	CKD 5D	CKD 2–3	CKD 4–5	CKD 5D	CKD 2	CKD 3	CKD 4–5	CKD 5D
Dietary intake	0.5–3	0.5–3	0.5–2	1–3	1–3	1–3	6–12	6	3–4	3–4
Height or length-for-age percentile or SDS	0.5–1.5	0.5–1.5	0.5–1	1–3	1–2	1	3–6	3–6	1–3	1–3
Height or length velocity-for-age percentile or SDS	0.5–2	0.5–2	0.5–1	1–6	1–3	1–2	6	6	6	6
Estimated dry weight and weight-for-age percentile or SDS	0.5–1.5	0.5–1.5	0.25–1	1–3	1–2	0.5–1	3–6	3–6	1–3	1–3
BMI-for-height-age percentile or SDS	0.5–1.5	0.5–1.5	0.5–1	1–3	1–2	1	3–6	3–6	1–3	1–3
Head circumference-for-age percentile or SDS	0.5–1.5	0.5–1.5	0.5–1	1–3	1–2	1–2	N/A	N/A	N/A	N/A
nPCR	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	1[a]

[a] *Only applies to adolescents receiving HD.*

BMI, Body mass index; *HD*, hemodialysis; *N/A*, not applicable; *nPCR*, normalized protein catabolic rate; *SDS*, standard deviation score.

Evaluation of nutrient intake

Dietary recall and food intake records kept in a diary are the two most common methods used for estimating nutrient intake [31,32]. The dietary recall (usually obtained for the previous 24 hours) is a simple, rapid method of obtaining a crude assessment of dietary intake. Since it relies on the patient's (or their parents) memory, the responses may not always be valid. However, the advantages to the recall method are that respondents usually will not be able to modify their eating behavior in anticipation of this dietary evaluation, and they do not have to be literate to provide the information. The most important limitation of the 24-hour recall method is its poor ability to capture the day-to-day variability in dietary intake. Children may be even more susceptible to this limitation than adults because they tend to exhibit more day-to-day variability [33]. Therefore it may be useful to obtain three 24-hour recalls (preferably, including one weekend day) to more completely evaluate the food intake pattern. A trained dietitian can obtain useful information from patients by using various models of foods and measuring devices to estimate food portion sizes.

Dietary diaries are prospective written reports of foods eaten during a specified length of time, characteristically 3−4 days, including a weekend day. A food intake diary provides a more reliable estimate of an individual's nutrient intake than do single-day records. The actual number of days chosen to collect food records should depend upon the degree of accuracy needed, the day-to-day variability in the intake of the nutrient being measured, and the cooperation of the patient. Records kept for more than 3 days increase the likelihood of inaccurate reporting because an individual's motivation will typically decrease with an increasing number of days of dietary data collection, especially if the days are consecutive [34].

Food records must be maintained meticulously to maximize the accuracy of the diary. Food intake should be recorded at the time the food is eaten to minimize any reliance on memory. Recording errors can be minimized if proper directions on how to approximate portion sizes and servings of fluid are provided. The dietitian should carefully review the food record with the patient for accuracy and completeness shortly after it is completed. While dietary diaries have been shown to give unbiased estimates of energy intake in normal-weight children younger than 10 years, underreporting is common in adolescents [35,36]. Accordingly, 24-hour recalls may be better suited to adolescents. The intake of calories, macronutrients (carbohydrate, protein, and fat), vitamins, and minerals derived from interviews or diaries is typically calculated using computer-based programs.

The food frequency questionnaire (FFQ), is another widely adopted method used to assess dietary intake [37]. The FFQ contains a number of food items (usually >80) that are typically consumed by the cohort being tested, to which the respondent indicates the frequency of consuming a serving of each item over the prior 28 days. The reported frequency of consuming any particular food item is divided by 28 to obtain a daily consumption frequency. For each item included in the FFQ, a reference value is available for the standard portion size by age, and for the average nutrient and energy level based on a review of several existing databases and references. The specific daily nutrient or caloric intake for a particular food item can then be calculated by the following formula: daily consumption frequency × standard portion size × average nutritional value. Total energy and all other nutrient levels are determined by summing the values obtained for each individual food item.

Physical measurements (anthropometry)

The evaluation of anthropometric parameters is a fundamental component of the nutritional assessment in pediatrics and must be accurately measured using calibrated equipment according to standardized techniques and, ideally, by the same person on each occasion [30,38,39]. Recumbent length, height, weight, and head circumference are measured directly, and BMI is calculated as weight (kg) divided by height (m) squared; reference values are available for children older than 2 years of age [40,41]. It is important to note that serial measurements are necessary for the assessment of growth.

Once measured, weight, length/height, head circumference, and BMI should be plotted on the appropriate growth chart, specific for the patient's age and sex. For premature infants the growth parameters should be plotted after correcting for their gestational age until they are 2 years old. In 2000 the center for disease control (CDC) published revised North American growth reference charts for infants and children up to 20 years of age [42], and in 2006 the World Health Organization (WHO) released new growth standards for children from birth to 5 years of age [43]. The WHO growth *standards* are distinguished from the CDC *reference* charts in two important ways. First, the children contributing to the WHO Growth Standards were specifically selected to represent children growing under ideal conditions, that is, they had nonsmoking mothers, were from areas of high socioeconomic status, and received regular pediatric healthcare, including immunizations. In addition, a subset of 882 infants, all breastfed for at least 4 months, provided longitudinal data for 24 months. Second, the study population was of broad ethnic diversity. In turn, an important observation made was that ethnicity had very little impact on growth, indicating that the growth standards reflect a reasonable expectation for growth regardless of ethnicity; only 3% of the variability in growth within the population could be attributed to country of origin [43].

Because the WHO Growth Standards represent ideal growth and ideal growth should be the goal for children with CKD as well, the WHO Growth Standards should be used as the reference for children from birth to 2 years. Thereafter, the differences between the CDC reference curves and the WHO Growth Standards are minimal. For this reason and because the switch is made from length to height measurement at 2 years, this appears to be a reasonable age to make the transition from the WHO Growth Standards to the CDC reference curves [30]. The growth pattern in several specific disorders such as Trisomy 21 (Down syndrome), Turner syndrome, or Marfan syndrome is altered in such a way that it is noticeably and consistently different than what is expected in the general population. For several specific disorders, sufficient data have been gathered to produce meaningful norms tailored specifically to populations with such conditions. Condition-specific growth charts should be used for these children [44].

In the general population, undernutrition is defined as weight-for-age, height-for-age, and weight-for-height more negative than −2.0 SD from the reference median [45]. It is important to recognize that the weight-for-age SDS is not particularly useful in isolation as weight-for-age will be low in growth-retarded children. Therefore it should be interpreted in the context of the height-for-age SDS. Accordingly, BMI is an accepted and standard method of assessing weight relative to height [46]. However, BMI is not completely independent of either age or height because of age-related changes in body proportions. For this reason, BMI is expressed relative to age in developing children [47], where age functions as a surrogate for both height and maturation. In children with CKD, in whom growth retardation and delayed maturation are common, this approach has limitations. Expressing BMI relative to chronological age in a child with growth and/or maturational delay will result in inappropriate underestimation of his or her BMI compared with peers of similar height and developmental age. To avoid this problem, it may be preferable to express BMI relative to height age (the age at which the child's height would be on the 50th percentile) in children with CKD [48]. This approach ensures that children with CKD are compared with the most appropriate reference group: those of similar height and maturation. However, caution must be used in applying this approach to children outside the pubertal or peripubertal period, for whom the correlation between height age and maturation is less clear. BMI relative to chronological age may be more logical in some cases, particularly when sexual maturation is complete.

In addition to absolute values, all anthropometric measurements should be expressed in terms of SDS, (also known as *z* score). An SDS within two standard deviations of the mean encompasses 95% of healthy children; an SDS greater than +2.0 or more negative than −2.0 is abnormal and mandates further evaluation.

Recumbent length is measured in children up to approximately 2 years of age or in older children who are unable to stand without assistance. Height is measured when the child is able to stand unassisted, usually by 2−3 years of age. As recumbent length overestimates height by an average of 0.7 cm with greater variation likely in taller children, the timing of when the length measurement is changed to height measurement should be noted on the growth chart [49]. In older children who are unable to stand, arm span can be used as a surrogate measure of height, although it may slightly underestimate the standing height [50].

Weight should be measured while the child is nude (young infants) or with very light clothing. Special attention should be devoted to patients with edema or who are undergoing maintenance dialysis, since changes in weight are more reflective of shifts in fluid balance than true weight gain or loss. It is important to determine the patient's "dry weight," which can be challenging as growing children are expected to gain weight. Five parameters are helpful for this estimate: measured weight, presence of edema, blood pressure, laboratory data, and the dietary interview. The mid-week, postdialysis weight is used for evaluation purposes in the hemodialysis (HD) patient, and the weight at a monthly visit (minus dialysis fluid in the peritoneal cavity) is used for the child receiving PD. A careful physical examination should be conducted to look for edema in the periorbital, pedal, and other regions of the body. Hypertension that resolves with dialysis is generally indicative of excess fluid weight. Decreased serum sodium, hemoglobin, and albumin levels may be markers of overhydration. Likewise, a rapid weight gain in the absence of a significant increase in reported energy intake or decrease in physical activity must be critically evaluated before it is assumed to be dry weight gain.

The head circumference should be measured in all children up to 24 months of age (or up to 36 months of age if appropriate centile charts are available) with a firm, nonstretchable tape. The tape is placed just above the supraorbital ridges and over the most prominent point on the occiput as the maximum head circumference to the nearest 0.1 cm is recorded.

Some of the previously recommended anthropometric measurements such as triceps skinfold thickness (TSF) and midarm circumference (MAC) used to calculate midarm muscle circumference and midarm muscle area were excluded from the 2008 KDOQI Pediatric Nutrition Guidelines [30] as skinfold thickness measurement is extremely operator dependent and lacks precision [51] and in the presence of fluid overload, both MAC and TSF are also likely to be overestimated [48]. However, there is renewed interest in measuring the midupper arm circumference (MUAC) to assess muscle mass, as muscle wasting is recognized as an integral component of PEW. The MUAC is measured to the nearest 0.1 cm using a nonstretchable flexible steel tape to measure the midpoint between the acromion and the olecranon process. While MUAC has the potential to offer a simple, low-resource alternative or supplement to BMI in assessing the nutritional status, no studies on the use of this measure in children with CKD have been published to date.

Special studies of protein catabolism

Protein equivalent of total nitrogen appearance (PNA), which is sometimes inappropriately referred to as protein catabolic rate (PCR), is a useful tool for the indirect estimation of DPI. It is based on the simple principle that during steady-state conditions, total nitrogen losses are equal to or slightly less than the total nitrogen intake [52]. While the majority of nitrogen losses (approximately 65%) occur as urea excretion in urine and/or dialysate [53], nitrogen is also lost as nonurea nitrogen in creatinine, uric acid, feces, skin, and hair. When scaled to body weight, the nonurea nitrogen excretion in children is more than in adults and likely varies by age as dialysate protein losses (per kg) during PD are highest in the youngest patients [53–56]. Protein loss in urine and/or dialysate is an additional source of nitrogen loss. The total nitrogen losses from the body are represented as total nitrogen appearance (TNA). The PNA can, in turn, be estimated by multiplying the TNA by 6.25 based on the fact that the nitrogen content of protein is relatively constant at 16%. Recognizing the practical difficulties associated with the measurement of all sources of nitrogen loss, in addition to the fact that a portion of these losses (e.g., hair and skin) are small and fixed, several researchers have attempted to derive quantitative relationships between TNA and the easily measurable and most abundant source of nitrogen loss, urea nitrogen [53–57].

As protein requirements are primarily determined from fat-free, edema-free body mass, PNA is usually normalized (nPNA) to some function of body weight. The usual weight used to nPNA is derived from the urea distribution space ($V_{\mathrm{urea}}/0.58$), as this idealized weight does not include the body fat weight.

Several important limitations of PNA should be recognized with respect to its usage in pediatrics. PNA is known to approximate protein intake only when the patient is in nitrogen equilibrium. However, because of growth, children are in an anabolic state and the PNA will, therefore, typically underestimate the actual DPI. It has also been demonstrated that children treated with recombinant human growth hormone may have a significantly increased DPI without exhibiting greater nitrogen excretion, reflective of an anabolic state [53]. On the other hand, in the catabolic patient, child or adult, PNA will exceed protein intake to the extent that there is net degradation and metabolism of endogenous protein pools to form urea. Therefore PNA can fluctuate from day-to-day and a single measurement of PNA may not reflect the usual protein intake. Additionally, PNA estimates have been found to be inaccurate at extremes of protein intake [58,59].

In patients undergoing maintenance HD, the normalized PCR (nPCR), which is equivalent to nPNA, is measured and it is dependent upon the urea generation rate (G) during the interdialytic period [60]. While the nPCR can be calculated simultaneously during formal Kt/V estimations by urea kinetic modeling, a simple algebraic formula used in pediatric HD patients [61] has been shown to yield nearly identical nPCR results:

$$\mathrm{nPCR} = 5.43 \times {}_{\mathrm{est}}G/V_1 + 0.17$$

where V_1 is total body water (in $L = 0.58 \times$ postdialysis weight in kg), and ${}_{\mathrm{est}}G$ is calculated as:

$${}_{\mathrm{est}}G(\mathrm{mg/min}) = \frac{[(C_2 \times V_2) - (C_1 \times V_1)]}{t}$$

where C_1 and V_1 are postdialysis BUN (mg/dL) and total body water (in $dL = 5.8 \times$ postdialysis weight in kg), respectively, from the previous HD treatment; C_2 and V_2 are predialysis BUN (mg/dL) and total body water (in $dL = 5.8 \times$ predialysis weight in kg), respectively, from the current HD treatment, and t is time (minutes) from the end of one dialysis treatment to the beginning of the next treatment.

A pediatric study demonstrated that an nPCR < 1 g/kg per day of protein predicted a sustained weight loss of at least 2% per month for 3 consecutive months in adolescent and young adult–aged patients receiving HD whereas serum albumin levels could not [62]. However, in younger pediatric HD patients, neither nPCR nor serum albumin level was effective in predicting weight loss [62].

It should be noted that the measurement of PNA is difficult in children receiving PD and is not considered a valid marker of their nutritional status. Therefore it has not been recommended as a standard nutritional assessment parameter by KDOQI [30].

Other measures

Serum albumin: Serum albumin was recommended in the 2000 KDOQI Nutrition Guidelines [63] as a marker of nutritional status because PEM may lead to hypoalbuminemia. Many studies have shown that hypoalbuminemia present at the time of dialysis initiation, as well as during the course of chronic dialysis, is a strong independent predictor of patient morbidity and mortality [64–68]. However, despite its clinical utility, serum albumin levels may be insensitive to short-term changes in nutritional status, do not necessarily correlate with changes in other nutritional parameters, and can be influenced by nonnutritional factors such as infection/inflammation, hydration status, peritoneal or urinary albumin losses, and acidemia [69,70]. Therefore while hypoalbuminemia remains an important component of the general evaluation of patients with CKD, it's value as an exclusive marker of nutritional status is questionable.

Bioelectrical impedance analysis (BIA): BIA is an attractive, noninvasive, and painless tool that can be used for estimating body composition with minimal operator training. Empiric equations have been developed for predicting extracellular, intracellular, and total body water volumes, as well as body cell mass, fat-free mass, and body fat content. In contrast to BIA that uses a single frequency, bioimpedance spectroscopy measures multiple frequencies for bioimpedance analysis and can provide better estimates of body composition [71,72]. It should be noted, however, that while these techniques allow for an accurate assessment of fat-free mass in healthy children, the estimate of fat-free mass of dialysis patients may be confounded by variations in hydration.

Dual-energy X-ray absorptiometry (DEXA): Whole-body DEXA is a reliable, noninvasive method to assess the three main components of body composition: fat mass, fat-free mass, and bone mineral mass/density. The accuracy of DEXA is minimally influenced by the variations in hydration that commonly occur in patients on dialysis. Studies of DEXA in this patient population have demonstrated its superior precision and accuracy when compared to anthropometry, total body potassium counting, creatinine index, and bioelectrical impedance [73,74]. The main limitations to DEXA in pediatrics are its substantial cost and the lack of reliable normal values in children on dialysis.

Subjective global assessment (SGA): The SGA, a method of nutritional assessment using clinical judgment rather than objective measures, has been validated for assessment of the nutritional status of adults with ESKD [75]. An SGA specific for the pediatric population has been validated in children undergoing major surgery [76], but its validity in children with CKD has not been established [77]. Appetite assessment is an integral part of the SGA and has also recently been incorporated into a study of children with CKD. In 879 participants of the CKiD study, a glomerular filtration rate (GFR) of <30 mL/min per 1.73 m^2 was associated with a 4.46 greater odds of having a worse appetite than those with a GFR $>$ 90 [78]. While appetite was not able to predict changes in height, weight, or BMI *z*-scores, patients not reporting a very good appetite had more hospitalizations over the next year when compared to those who reported having a very good appetite [78]. Finally, in 2001, the malnutrition–inflammation score (MIS) was introduced as one of the CKD-specific nutritional scoring systems, which incorporates seven components of the original SGA plus BMI, serum albumin level, and total iron-binding capacity or transferrin level. In adult patients receiving HD, the MIS is strongly associated with inflammation, nutritional status, quality of life, and 5-year prospective mortality [79].

Nutrition-focused physical examination: The so-called nutritional physical examination involves visual assessment and physical palpation of potential areas of fat or muscle wasting, to assess nutritional status. The presence of pitting edema can help differentiate between measured weight and the child's euvolemic weight. A careful examination of the tongue, skin, teeth, breath, and hair may provide important clues suggestive of nutrient deficiency or excess [80] that can be confirmed by appropriate laboratory testing.

Nutritional requirements

The nutritional requirements for children with CKD and those undergoing maintenance dialysis are generally based on the published recommended dietary allowances (RDA) for healthy children [81]. However, it is important to recognize that the RDA's are estimates of the average needs of the normal population, are meant to be applied to children as a group, and do not take into account the specific requirements of an individual patient. The American Academy of Pediatrics' Committee on Nutrition states that RDAs cannot be used as a measure of nutritional adequacy in children [82].

The basis for the RDA values varies for different nutrients. While the RDA for energy reflects the average energy intake needed to maintain body weight and activity of well-nourished normal-sized individuals (with an additional provision for infants and children to ensure normal growth), the RDAs for protein are based on protein nitrogen loss (mean + 2 SD) and are further adjusted to account for poor protein quality and individual variability.

The RDAs for a number of nutrients have been replaced by dietary reference intakes (DRIs) [83]. The DRIs are comprised of a set of four reference values: *estimated average requirement* (EAR), *recommended dietary allowance (also popularly known as recommended daily allowance)* (RDA), *adequate intake* (AI), and *tolerable upper intake level* (UL). The EAR is the median usual intake value that is estimated to meet the requirements of half of the healthy individuals in a specific age and gender group, while the other half of individuals are at risk for nutritional deficiency and/or chronic disease. EARs are used to assess the prevalence of nutrient inadequacy in a group of individuals. RDAs are intake levels that, according to the available scientific evidence, meet the nutrient requirement of almost all ($>97\%$) healthy individuals in a specific age and gender group. AI values are used when the scientific evidence is lacking to establish an EAR or an RDA. AIs are derived either from experimental data or are approximated from the observed mean nutrient intakes of apparently healthy people. The UL is the highest level of daily nutrient intake that is likely to pose no risk of adverse health effects in almost all individuals in a specified group. The UL is not intended to be a recommended intake level and the potential risk for adverse effects increases if the intake exceeds the UL.

Because multiple national and international bodies have published slightly different recommended values and have used terms that are not directly comparable, the PRNT decided to take a more pragmatic approach and has recently introduced the novel term suggested dietary intake (SDI), which comprises a range of values [84]. With reference to energy requirements, the lower and upper limits of the SDI fall within the lower and upper values of the previously published works that describe the average energy requirement (daily amount of energy considered sufficient to meet the needs of half the population). The lower and upper limits of the SDI for protein fall within the average amount +2 SD given in the published values [i.e., the daily amount of protein considered sufficient to meet the needs for nearly all (97.5%) of the population] [84].

Energy requirements

Energy requirements are determined by lean body mass; are modified by growth, current nutritional status, and physical activity; and are influenced by genetics, ethnicity, and environment. The optimal energy intake from food should maintain normal body mass, promote growth and development, and support the level of physical activity performed by the subject. Recommendations for energy intake come from observational and experimental studies, and more recently from studies using doubly labeled water (DLW) along with a factorial method to address physical activity [85]. The DLW technique is considered the "gold standard" for assessing total energy expenditure (TEE), which includes physical activity energy expenditure (the most variable component of TEE), resting energy expenditure (REE), and the thermic effect of food.

Studies that have investigated the optimal requirements for energy in children with CKD found no difference in the REE (also known as basal metabolic rate) between these children and healthy children, after adjusting for lean body mass [86]. Most studies have reported that a dietary energy intake of around 100% of the estimated energy requirement (EER) in children with CKD resulted in acceptable growth. A large, prospective trial enrolled 65 children aged 2–16 years with an estimated glomerular filtration rate (eGFR) $<75\ \text{mL/min per } 1.73\ \text{m}^2$ and showed that growth was normal with median energy intakes of 94%–98% of EAR at baseline and 85%–94% of EAR at 2 years of follow-up in the 51 subjects who completed the study [87].

To date, energy requirements for children with CKD have been considered to be 100% of the EER for chronological age, with further adjustment to energy intake individualized and based upon response in terms of the rate of weight gain or loss that is individually adjusted for the physical activity level and BMI [83,88] (Tables 34.3 and 34.4). Energy requirements for patients treated with maintenance HD or PD are similar to those of predialysis patients. In children receiving maintenance PD therapy, variable glucose absorption takes place from the dialysis fluid depending on the PD modality, dialysate glucose concentration, and peritoneal membrane solute transport capacity [89]. In a study of 31 children older than 3 years on ambulatory PD therapy, the mean energy intake derived from peritoneal glucose absorption was 9 kcal/kg per day [90]. Since many children who receive chronic PD are underweight, the prescribed energy intake in them should exclude the estimated calorie absorption from the dialysate as failure to do so may compromise the nutritional quality of the diet. However, some children—and particularly infants receiving PD therapy—gain weight at a faster rate than normal despite oral and/or enteral energy intakes that are lower than the average requirements. Reduced physical activity and increased exposure to high dialysate glucose concentrations for fluid removal may be

TABLE 34.3 Equations to estimate energy requirements (EERs) for children at healthy weights.

Age	EER (kcal/d) = total energy expenditure + energy deposition
0–3 months	$\text{EER} = [89 \times \text{weight (kg)} - 100] = 175$
4–6 months	$\text{EER} = [89 \times \text{weight (kg)} - 100] = 56$
7–12 months	$\text{EER} = [89 \times \text{weight (kg)} - 100] = 22$
13–35 months	$\text{EER} = [89 \times \text{weight (kg)} - 100] = 20$
3–8 years	
Boys	$\text{EER} = 88.5 - 61.9 \times \text{age (year)} + \text{PA} \times [26.7 \times \text{weight (kg)} + 903 \times \text{height (m)}] + 20$
Girls	$\text{EER} = 135.3 - 30.8 \times \text{age (year)} + \text{PA} \times [10 \times \text{weight (kg)} + 934 \times \text{height (m)}] + 20$
9–18 years	
Boys	$\text{EER} = 88.5 - 61.9 \times \text{age (year)} + \text{PA} \times [26.7 \times \text{weight (kg)} + 903 \times \text{height (m)}] + 25$
Girls	$\text{EER} = 135.3 - 30.8 \times \text{age (year)} + \text{PA} \times [10 \times \text{weight (kg)} + 934 \times \text{height (m)}] + 25$

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TABLE 34.4 Physical activity coefficients for determination of energy requirements in children ages 3–18 years.

	Level of physical activity			
Gender	Sedentary	Low active	Active	Very Active
	Typical ADL only	ADL + 30–60 min of daily moderate activity (e.g., walking at 5–7 km/h)	ADL + ≥60 min of daily moderate activity	ADL + ≥60 min of daily moderate activity + an additional 60 min of vigorous activity or 120 min of moderate activity
Boys	1.0	1.13	1.26	1.42
Girls	1.0	1.16	1.31	1.56

ADL, Activities of daily living.
Adapted and reproduced from Health Canada. Dietary reference intakes, http://www.hc-sc.gc.ca/fn-an/alt_formats/hpfb-dgpsa/pdf/nutrition/dri_tables-eng.pdf, with permission from the Minister of Health, Health Canada 2020, © All rights reserved.

explanations; in these cases the calorie contribution from dialysate should be taken into account when estimating energy requirements, especially in the setting of obesity.

Historically, a number of studies have shown that the majority of pediatric patients with CKD exhibit an inadequate dietary energy intake [91–93] in association with worsening kidney function [93]. In a large, prospective study of growth failure in children with CKD, caloric intakes were <80% of the RDA for age in more than one-half of food records obtained [94]. While inadequate voluntary energy intake has been clearly demonstrated in infants with CKD [95,96], energy intakes for older children are generally normal relative to their body size [94]. In contrast to prior publications, the recent assessment of dietary intake in children with CKD from the CKiD study revealed that the median energy consumption levels were higher than the recommended values in all age-groups, implying that at least half of the kids in each age-group consumed more than the recommended value. While there was a decreased energy consumption with the fall in GFR ($P = .003$), younger children were more likely to exceed the recommended caloric intake than their older counterparts ($P < .001$) [97].

Since energy intake is the principle determinate of growth during infancy, normally a period of very rapid growth, malnutrition has the most marked negative effect on growth in children with congenital disorders leading to CKD and can rapidly lead to the loss of as much as 2 SDS for length [98]. More than half (58.3%) of infants with CKD in the 2008 NAPRTCS report had a height SDS worse than −1.88 (mean for all infants: −2.34) [99]. However, maximizing caloric intake has been noted to be particularly effective in improving height velocity only in infants with CKD or receiving dialysis [95,96,98]. As children older than 2 years of age with CKD do not generally experience catch-up growth [100], the provision of adequate energy intake early in life is crucial. Rizzoni et al. [19] demonstrated that the growth of infants with CKD receiving ≤100% of the RDA averaged 53% (range 10%–72%) of expected, whereas it averaged 97% (range 61%–130%) of expected during periods when the energy intake was ≥100% of the RDA. In a study of 35 children younger than 5 years with CKD stages 4–5, significant weight gain and accelerated linear growth were demonstrated in those starting enteral feeding at <2 years of age, while improved weight gain and maintenance of growth velocity were observed in those starting enteral feeds at age 2–5 years, in each case without exceeding normal energy requirements [95]. If children younger than 3 years with a length (or height) for age <−1.88 SDS fail to achieve expected weight gain and growth when receiving an intake based on chronological age, estimated requirements may be increased by using height age–related recommendations.

While worldwide, undernutrition in children with CKD remains a concern, recent data from the IPPN registry reported a 19.7% prevalence of overweight/obesity (compared with 8.9% underweight) in children at the start of the chronic PD [12]. Overweight/obesity is particularly common in North America with prevalence rates of approximately 60% in 2- to 5-year-old children with ESKD and over 20% in all other age-groups. Multivariate analysis revealed that nasogastric/gastric tube feeds was an independent predictor of overweight/obesity [101]. Ku et al. [102] analyzed data from the US Renal Data System from over 13,000 children ages 2–19 years old with ESKD who initiated dialysis 1995 and 2011 and found that whereas the prevalence of underweight children decreased from 12% to 9%, the prevalence of obesity increased from 14% to 18% during the study period. Accordingly, prevention and treatment of obesity in patients with CKD is important. Energy requirements for overweight or obese children are lower than normal and can be estimated by using equations specific for children heavier than a healthy weight [83].

Protein requirements

The usual DPI requirement is based on the nitrogen losses in the urine, stool, hair, and nails, in addition to the extra protein needed for growth [103]. It is important that the required protein intake be accompanied by adequate sources of nonprotein energy (i.e., carbohydrates and fats) as inadequate caloric intake results in the inefficient use of dietary protein as a calorie source, with a resultant increased generation of urea. Thus ensuring that caloric needs are met is an important step in assessing protein requirements and modifying recommended protein intake. It is advised that at least 50% of the total protein intake consist of protein of high biologic value such as the protein from milk, eggs, meat, fish, and poultry. However, more recently, it has been argued that plant-based proteins are not only nutritionally adequate but have other beneficial effects that may favor their use in CKD patients [104].

The 2009 KDOQI Pediatric Nutrition Guidelines recommended maintaining the DPI at 100%–140% of the DRI for ideal body weight in children with CKD stage 3 and at 100%–120% of the DRI in children with CKD stages 4–5 (Table 34.5) [30]. Since the publication of the KDOQI guidelines, there have been no studies that support modifying abovementioned statements. At the same time, the recently published PRNT–CPR [17] suggests that the target protein intake in children with CKD 2–5D should be at the upper end of the recommended intake to promote optimal growth, and the DPI should not be reduced below the lowest end of the recommended range that is considered the minimum safe amount.

TABLE 34.5 Recommended dietary protein intake in children with chronic kidney disease (CKD) stages 3–5 and 5D [30].

Age	DRI (g/kg per day)	Recommended for CKD stage 3 (g/kg per day) (100%–140% DRI)	Recommended for CKD stages 4–5 (g/kg per day) (100%–120% DRI)	Recommended for HD (g/kg per day)[a]	Recommended for PD (g/kg per day)[b]
0–6 months	1.5	1.5–2.1	1.5–1.8	1.6	1.8
7–12 months	1.2	1.2–1.7	1.2–1.5	1.3	1.5
1–3 years	1.05	1.05–1.5	1.05–1.25	1.15	1.3
4–13 years	0.95	0.95–1.35	0.95–1.15	1.05	1.1
14–18 years	0.85	0.85–1.2	0.85–1.05	0.95	1.0

[a] *DRI + 0.1 g/kg per day to compensate for dialysis losses.*

[b] *DRI + 0.15–0.3 g/kg per day depending on patient age to compensate for peritoneal losses.*

DRI, Dietary reference intake; *HD*, hemodialysis; *PD*, peritoneal dialysis.

As there is a nearly linear relationship between protein and phosphorus intake [105], the consumption of a high-protein diet in patients with CKD is frequently associated with the development of hyperphosphatemia [106]. Conversely, low-protein diets decrease the development of hyperphosphatemia, metabolic acidosis, hyperkalemia, and other electrolyte disorders. However, pediatricians are rightly concerned about the potential for harmful effects of severe dietary protein restriction, particularly as it pertains to the growth of infants and young children with CKD. Two randomized controlled trials have compared low-protein versus normal-protein diets in children with CKD [107,108]. In a study of 24 infants with eGFR $<55\,\mathrm{mL/min}$ per $1.73\,\mathrm{m}^2$, a significantly lower SDS for length and height velocity was seen in the group of patients randomized to receive a low-protein formula (1.4 ± 0.3 g/kg per day) as compared to those who received a DPI of 2.4 ± 0.4 g/kg per day [107]. In the second and largest pediatric trial evaluating protein intake, 191 children (2–18 years) with CKD stages 3–4 were randomized to a reduced DPI of 100% RDA (0.8–1.1 g/kg ideal body weight) or an unrestricted intake (mean DPI—181% RDA). This modest reduction in protein intake, with maintenance of energy intake greater than 80% RDA in both groups, did not adversely affect growth, serum albumin, or the rate of CKD progression within the observation period of 2–3 years. Hence, although there is no evidence for a nephroprotective effect of dietary protein restriction, this study did provide evidence that DPI can be safely restricted to 0.8–1.1 g/kg per day in children older than 2 years with CKD [108].

While the spontaneous DPI is reduced in association with CKD progression in a manner similar to that of energy intake, the DPI typically still remains far in excess of the average requirements, ranging from 150% to 200% of the RDA [92,94,108]. The recent assessment of dietary intake from the CKiD study revealed that the median protein intake exceeded the recommended levels in all age-groups, particularly among younger participants [97].

There are situations in which the dietary protein requirements may be increased relative to the general recommendations. This is the case in patients with ongoing proteinuria or during recovery from intercurrent illness, and the recommended intake may be adjusted to height age instead of chronological age if evidence of protein deficiency exists or persists. Modification of protein recommendations may also be necessary in obese children. Obese individuals have a greater percentage of body fat, which is much less metabolically active than lean body mass. Therefore it is believed that basing protein (and energy) requirements of obese individuals on their actual weight may overestimate requirements. Conversely, the use of ideal body weight as a reference for an obese person does not take into account the increase in body protein needed for structural support of extra fat tissue. Therefore a common practice is to estimate protein requirements of obese individuals based on an "adjusted" weight (i.e., adjusted weight = ideal weight for height + 25% × [actual weight − ideal weight], where 25% represents the percentage of body fat tissue that is metabolically active) rather than their actual body weight [109].

Additionally, the optimal protein intake for pediatric patients on maintenance dialysis (CKD 5D) has not yet been well defined. Reviews of nitrogen-balance studies performed in adult dialysis patients with different protein intakes conclude that HD patients are in neutral nitrogen balance with a protein intake as low as 0.75–0.87 g/kg per day, and PD patients with a protein intake of 0.9–1.0 g/kg per day [110–114]. A single nitrogen-balance study has been performed in dialyzed children [90]. In 31 pediatric patients receiving automated PD, the investigators observed a positive correlation between nitrogen balance and DPI ($r = 0.671$, $P = .0001$) and total energy intake ($r = 0.489$, $P = .001$) and concluded that the DPI should be at least 144% of RDA, and total energy intake 89% of the RDA, to achieve an estimated nitrogen balance of >50 mg/kg per day. A single randomized prospective study in adults [115] and several trials in children [116–118] have addressed the effect of selectively increasing the amino acid supply in patients on PD therapy. Despite increases in amino acid and DPI, no significant beneficial effects on nutritional status and longitudinal growth were achieved by this intervention in children, whereas the urea concentration frequently increased. These results are compatible with the interpretation that it is not possible to induce tissue anabolism by selectively increasing protein and amino acid ingestion, except in subjects with subnormal baseline protein intake. If more protein is ingested than needed for metabolic purposes, all the excess is oxidized and results in the accumulation of nitrogenous-containing end products.

Although dialyzed children require larger amounts of protein per unit of body weight compared to adults to grow in size and lean body mass, this demand is fully accounted for by the age-adjusted pediatric DRI. Hence, the only additional dietary protein requirement justified by evidence is the replacement of dialytic nitrogen losses. In those on long-term PD therapy, daily peritoneal protein losses decrease with age across childhood from an average of 0.28 g/kg in the first year of life to less than 0.1 g/kg in adolescents [119]. Peritoneal amino acid losses add approximately one-third to the nitrogen lost with protein, resulting in a total additional dietary protein requirement ranging from 0.15 to 0.35 g/kg, depending on patient age

(Table 34.5). Patients with high-peritoneal transport characteristics tend to have low serum albumin levels, likely due to increased peritoneal protein losses; these patients may have slightly greater protein requirements. Because dialytic protein concentrations can be measured easily, consideration should be given on occasion to monitoring of peritoneal protein excretion and individual adaptation of the dietary protein prescription according to actual peritoneal losses.

Amino acid and protein losses during HD vary according to dialyzer membrane characteristics and reuse. Whereas losses have not been quantified in children, an average of 8–10 g of amino acids and less than 1–3 g of protein are lost per HD session in adults [120–122]. On the basis of three HD sessions per week for a 70-kg adult, this equates to 0.08 g/kg per day. Assuming that dialytic amino acid losses are linearly related to urea kinetics, children can be expected to have similar or slightly higher amino acid losses than adults and an added DPI of 0.1 g/kg per day should be appropriate to compensate for pediatric HD losses.

Finally, there is some concern that a high DPI may prove to be harmful when consumed by dialyzed children. In a DXA study of body composition in 20 children on long-term PD therapy with a mean DPI of 144% RDA, protein intake inversely correlated with bone mineral density, bone mineral content, fat-free mass, and plasma bicarbonate level, suggesting that a high protein intake may cause tissue catabolism and bone loss by worsening metabolic acidosis [123]. However, the most convincing argument for limiting DPI in dialyzed children is derived from the solid evidence supporting the key etiologic role that dietary phosphorus load has in the pathogenesis of dialysis-associated calcifying arteriopathy. As noted previously, there is a nearly linear relationship between protein and phosphorus intake [105], which results in the frequent association between high quantities of protein in the diet and hyperphosphatemia [124]. Hence, it appears most appropriate to limit DPI in children on dialysis to the safe levels known to ensure adequate growth and nutrition in healthy children. Additionally, the DPI may be adjusted to the lower end of recommended intake in patients with persistently high blood urea levels after other causes for high urea levels have been excluded.

Lipid requirements

Dyslipidemia is a frequently recognized complication of CKD in children [125,126], occurs relatively early in the course of CKD (i.e., stage 3 CKD), and increases in prevalence with decreasing kidney function [126–128]. Baseline data from the CKiD study reported the presence of dyslipidemia in 44% of 250 children with mild-to-moderate CKD; the most common abnormality was hypertriglyceridemia in 75% [129]. More recently, the CKiD study has reported the change in dyslipidemia with declining GFR and increasing proteinuria in 508 children (76% nonglomerular CKD, 24% glomerular CKD) [126]. The study showed that 35% of patients with nonglomerular CKD had dyslipidemia at baseline that increased significantly over time, while 43% of children with glomerular CKD had dyslipidemia at baseline that remained persistent over time. Declining GFR and worsening proteinuria were independently associated with worsening dyslipidemia [126]. The dyslipidemia seen in children with CKD has complex underlying metabolic alterations and is characterized by increased levels of serum triglycerides in combination with high levels of very-low-density lipoprotein (LDL) and intermediate-density lipoproteins, low levels of HDL particles, and normal or modestly increased levels of total and LDL cholesterol [125,128,130]. This pattern of dyslipidemia has been labeled “atherogenic.” In addition, hypertriglyceridemia has been shown to be an independent contributor to the development of CVD [131,132] and may also accelerate the progression of CKD [133].

While there is no direct evidence indicating that the measurement of lipid status will improve clinical outcomes, the 2013 KDIGO CPG for lipid management in CKD recommends obtaining a lipid profile (total, LDL, HDL cholesterol, and triglycerides) in all children with newly diagnosed CKD (including those receiving dialysis or with a kidney transplant), with annual follow-up measurements [134]. The optimal management of dyslipidemia in children with CKD is not clearly defined. Treatment of malnutrition related to impaired kidney function is essential and should supersede any potential rise in lipid levels that might result from it. On the contrary, prevention and treatment of obesity in patients with CKD is an important strategy to reduce the risk of hyperlipidemia [135]. Correction of metabolic acidosis, vitamin D therapy, and correction of anemia with erythropoietin each also seem to have some normalizing effect on dyslipidemia in children with CKD [136–138]. The KDOQI Dyslipidemia Guidelines’ recommendations [139], endorsed by the KDOQI Cardiovascular Guidelines [140] recommend that the dietary and lifestyle recommendations made for adults are also appropriate for postpubertal children and adolescents with CKD. Therapy with statins or statin/ezetimibe combination is not recommended for children with CKD (including those receiving dialysis or with kidney transplant) who are less than 18 years of age [134]. In 1992 the National Cholesterol Education Program Pediatric Panel Report [141] provided dietary recommendations for all children. These guidelines were later endorsed by the Expert Panel on Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents [142]. The latter publication recommends that in children with identified hypercholesterolemia, less than 25%–30% of calories should come from dietary fat, of which $\leq 7\%$ should be from saturated fatty acids; the daily cholesterol intake should be <200 mg. For serum triglyceride >150 mg/dL, therapeutic lifestyle changes are recommended along with a low-fat diet and a low intake of simple carbohydrates [134]. The child should be encouraged to ingest complex carbohydrates in lieu of simple sugars and concentrated sweets and to use unsaturated fats such as oils and margarines from corn, safflower, and soy. Plant stanol esters in the form of dietary supplements reduce intestinal cholesterol absorption and may provide a safe and effective means of reducing serum cholesterol.

High intakes of $n-3$ polyunsaturated fatty acids [omega-3 fatty acids ($n-3$ FA), docosahexaenoic acid (DHA), and eicosapentaenoic acid (EPA)] have been associated with decreasing TG levels and a decreased risk of heart disease [143,144]. Therefore EPA and DHA, found almost exclusively in fish and marine sources, must be provided in the diet; the best sources are fatty fish (e.g., tuna, mackerel, trout, salmon, herring, sardines, and anchovies) [145]. Although $n-3$ FAs have been found to be extremely safe by both Health Canada and the US Food and Drug Administration, there is insufficient evidence at this time to recommend routine use of $n-3$ FAs to treat hypertriglyceridemia in children with CKD.

Dietary fiber, particularly naturally occurring viscous fiber, reduces total and LDL cholesterol levels and high intakes have been associated with reduced rates of CVD. The AI for total fiber is based on daily caloric intake and is 14 g/1000 kcal per day for all children 1 year and older. Dietary fiber is found in most fruits, vegetables, legumes, and whole grains, which are foods restricted in low-potassium and low-phosphorus diets; therefore meeting normal daily fiber recommendations is challenging for children with CKD. Tasteless mineral- and electrolyte-free powdered forms of fiber (e.g., Unifiber, Benefiber) are available to add to meals or drinks if children are unable to meet their fiber intake by diet. High-fiber diets require additional fluid intake, which may not be possible for oliguric or anuric patients with a strict fluid restriction.

Bone mineral metabolism

Optimal control of bone and mineral homeostasis is essential, not only for the prevention of debilitating skeletal complications and the achievement of adequate growth, but also for the prevention of vascular calcification and cardiovascular disease. Complications of mineral bone disease (MBD) are, however, common and contribute to the high morbidity and mortality seen in children with CKD. The provision of adequate but not excessive amounts of calcium and phosphorus is thus an important part of CKD management.

Calcium

Adequate dietary calcium intake during childhood is necessary for skeletal development and acquisition of optimal peak bone mass [146]. The current recommendation is that patients with CKD should achieve a calcium intake of 100% of the DRI, just as their healthy peers (Table 34.6) [147]. While there are no studies to set a safe upper limit of calcium intake for healthy children, KDOQI suggested that 200% of the DRI is the safe upper limit for patients with CKD, as excess calcium is potentially detrimental and can lead to ectopic calcification [148]. Similarly, and in response to the epidemiological evidence linking higher calcium concentrations to increased mortality in adults with CKD, the 2017 KDIGO CPG update for the diagnosis, evaluation, prevention, and treatment of CKD-MBD suggests to avoid hypercalcemia in adult patients with CKD G3a-G5D [149]. In the

TABLE 34.6 Recommended calcium intake for children with chronic kidney disease (CKD) stages 2–5 and 5D [30].

Age	DRI	Upper limit (for healthy children)	Upper limit for CKD stages 2–5, 5D (dietary + phosphate binders[a])
0–6 months	210	ND	≤420
7–12 months	270	ND	≤540
1–3 years	500	2500	≤1000
4–8 years	800	2500	≤1600
9–18 years	1,300	2500	≤2500

[a] *Determined as 200% of the DRI, to a maximum of 2500 mg elemental calcium.*
DRI, Dietary reference intake; *ND*, not determined.

case of children with CKD, the Work Group suggested maintaining the serum calcium level in the age-appropriate normal range to meet the higher calcium requirements of the growing skeleton [149].

The main dietary sources of calcium for children are milk, milk products, breast milk, and manufactured infant formulas. Infants and young children usually meet the DRI for calcium with the consumption of adequate volumes of breast milk/infant formula. All standard and most specialized infant milk formulas have a higher concentration of calcium compared to human milk, but lower than cow's milk or the formulas intended for older children. Formulas designed for infants must comply with set compositional criteria, providing a minimum amount of 50–60 mg of calcium per 100 cal and a Ca:P ratio between 1.1 and 2.0 [150,151]. The calcium content of reduced-fat dairy products is comparable to whole milk-derived products. The "milk and milk products" food group (milk, cheese, yogurt, cream, and ice cream) contribute 44%–70% of dietary calcium intake, being highest in the younger age-groups. "Cereal and cereal products" (grains made into pasta, rice, breads, breakfast cereals, and biscuits) contribute 16%–28% of average daily calcium intake. Other sources of calcium, including vegetables, fish, meat, fruit, and confectionary, each contribute between 1% and 7% of daily calcium intake [18]. The variations in foods eaten in different countries or cultures may alter the relative calcium intake from specific food groups [18].

Most problematic is the fact that the largest sources of dietary calcium for most persons are dairy products that are also rich in phosphorus; in turn, phosphorus restriction in the patient with CKD universally leads to a decreased calcium intake. In these situations, calcium supplementation may be required as low phosphorus–, high calcium–containing foods such as collards, dandelion greens, kale, rhubarb, and spinach usually do not make up a substantial part of a child's diet. Several products fortified with calcium such as fruit juices and breakfast foods are commercially available, and limited studies have suggested that the bioavailability of calcium from these products is at least comparable to that of milk [152]. Calcium can also be supplemented in medicinal forms such as carbonate (40% elemental calcium), acetate (25% elemental calcium), and gluconate (9% elemental calcium) salts of calcium that are commonly used as phosphate binders. When used for calcium supplementation alone, ingesting these products between meals maximizes calcium absorption. Chloride and citrate salts of calcium should be avoided as the former may lead to acidosis in patients with CKD and the latter may enhance aluminum absorption.

The absorption of calcium from foods and medications (calcium-based phosphate binders and calcium supplements) is about 30% but varies between 5% and 82% depending on the food source and vitamin D status of the person. Milk, dairy products, and fortified food have a calcium bioavailability between 30% and 40%, whereas it is below 10% for vegetables and fruits (such as spinach and rhubarb). The calcium intake from phosphorus binders can contribute significantly to dietary calcium intake and should be included when calculating total daily calcium intake in CKD patients.

Excessive calcium intake in conjunction with activated vitamin D analogs can lead to (1) hypercalcemia, (2) adynamic bone disease, and (3) systemic calcification. Therefore the total calcium intake from diet and medications (including phosphate binders) should be within the DRI, and no more than twice the DRI, unless there are exceptional circumstances such as in infants with mineral-depleted bones. Accordingly, the KDOQI guidelines recommend that the combined elemental calcium intake from nutritional sources and phosphate binders should not exceed two times the DRI for age, except for ages 9–18 years (both genders) where two times the DRI (2600 mg) exceeds the UL of 2500 mg (Table 34.6) [30,147,148]. The serum level of total corrected calcium should be maintained within the normal range (8.8–9.5 mg/dL), preferably toward the lower end and definitely not more than 10.2 mg/dL.

The calcium balance in patients undergoing maintenance dialysis is also affected by the dialysate calcium concentration. The calcium balance during PD is usually negative with the use of a dialysate calcium concentration of 2.5 mEq/L and positive with a dialysate concentration of 3.0–3.5 mEq/L [153]. As a result, it may be wise to use a low calcium dialysate (2.5 mEq/L) in children undergoing dialysis who are receiving calcium-containing phosphate binders along with activated vitamin D sterols. On the contrary, a 3.0- to 3.5-mEq/L calcium dialysate should be used if hypocalcemia is present in a child with elevated parathyroid hormone (PTH) (>300 pg/mL) as part of the treatment of secondary hyperparathyroidism (SHPT) and may be needed in children restricted to noncalcium-containing phosphate binders only.

Phosphorus

In an effort to prevent/control CKD-associated MBD and CVD, serum phosphorus concentrations above the normal reference range for age (Table 34.7) should be avoided in patients with advanced CKD. However, even during the earlier stages of CKD when the serum phosphorus levels are typically within the normal range, the dietary phosphorus load is an

TABLE 34.7 Age-specific normal ranges of blood ionized calcium, total calcium, and phosphorus.

Age	Ionized calcium (mmol/L)	Calcium (mg/dL)	Phosphorus (mg/dL)
0–5 months	1.22–1.40	8.7–11.3	5.2–8.4
6–12 months	1.20–1.40	8.7–11.0	5.0–7.8
1–5 years	1.22–1.32	9.4–10.8	4.5–6.5
6–12 years	1.15–1.32	9.4–10.3	3.6–5.8
13–20 years	1.12–1.30	8.8–10.2	2.3–4.5

Conversion factor for calcium and ionized calcium: mg/dL × 0.25 = mmol/L. Conversion factor for phosphorus: mg/dL × 0.323 = mmol/L.
Adapted from National Kidney Foundation. KDOQI clinical practice guidelines for bone metabolism and disease in children with chronic kidney disease. Am J Kidney Dis 2005;46(Suppl. 1):S1–122.

important determinant of the severity of hyperparathyroidism. Dietary phosphorus restriction decreases PTH levels and increases 1,25(OH)$_2$D, whereas a dietary phosphorus intake approximately twice the DRI for age aggravates hyperparathyroidism despite little or no change in the serum phosphorus level (the result of elevated FGF-23 levels and enhanced phosphorus excretion) [154]. It is important to note that the higher physiological serum concentrations of calcium and phosphorus that are observed in healthy infants and young children presumably reflect the increased requirements for these minerals by the rapidly growing skeleton. Rickets due to phosphorus deficiency can occur in preterm infants whose diet provides insufficient quantities of phosphorus, as well as in infants and children with hypophosphatemia due to inherited disorders of renal phosphate transport. Hence, when dietary phosphorus is restricted to control hyperphosphatemia and SHPT in children with CKD, subnormal serum phosphorus values are equally important to avoid.

Data from the United States for all age-groups indicate that the highest contributors to phosphorus intake are milk, meat, and grains [155,156]. As with calcium intake, the highest percentage of dietary phosphorus comes from "milk and milk products" particularly in the younger age-groups, while "meat and meat products" account for 15%–20% of phosphorus intake, being highest in older children. Breast milk is relatively low in phosphate, having a concentration about one-half of most standard whey-based formulas and one-third of casein-based infant formulas. For standard infant formulas, only the minimum level (25–30 mg per 100 cal), but not the maximum level of phosphate is regulated [150,151]. Phosphate additives, such as phosphoric acid and sodium phosphate, are used by the food industry to improve the texture, taste, appearance, and shelf life of many processed foods and their presence, but not quantity, is usually indicated on the ingredient list [157]. It is important to note that the phosphorus additive is in the inorganic form that is readily absorbed, in contrast to the organic form of phosphorus present in natural food, and can significantly increase phosphorus intake. In addition, inorganic phosphates are added to several medications, such as antacids and many antihypertensive medications, as an excipient that aids in dispersion of the active drug ingredient once ingested [158]. The phosphorus load from medications can make a meaningful contribution to the daily phosphorus intake and, thus, should be reviewed carefully with members of the health-care team.

The absorption of phosphorus from food depends on whether it is in an organic or inorganic form. Meats, fish, dairy, vegetables, grains, and nuts contain organic carbon-bound phosphorus, with a bioavailability between 30% and 70%. Plant-based organic phosphorus (including seeds and legumes) is stored in the form of phytate or phytic acid, which cannot be broken down by humans, reducing the bioavailability to 30%–40%. However, as noted earlier, the bioavailability of inorganic phosphorus salts added to processed foods can be as high as 100% [18,157].

Current recommendations suggest that in children with CKD whose serum PTH concentration exceeds the target range but whose serum phosphorus concentration remains normal, the dietary phosphorus intake should be restricted to 100% of the DRI; in contrast, the intake should be restricted to 80% of the DRI when the serum phosphorus concentration exceeds the normal reference range for age (Tables 34.7 and 34.8) [88,148].

Despite the need to restrict dietary phosphorus, most clinicians recognize that an overly restrictive dietary phosphorus intake is not only often impractical, but it can be ill-advised as it may lead to an inadvertent poor DPI [60]. In addition, extremely low-phosphorus diets are typically unpalatable. Young infants are characteristically managed with a low phosphorus–containing milk formula such as Similac PM 60/40 (Abbott Nutrition), Renastart, (Vitaflo Nutrition), Renalcal (Nestle Health Sciences), or by pretreatment of breast milk, infant formula, and cow's milk with sevelamer carbonate (Renvela; Sanofi US) that can effectively reduce the phosphorus content in the supernatant by 80%–90%

TABLE 34.8 Recommended maximum oral and/or enteral phosphorus (mg/d) intake for children with chronic kidney disease (CKD).

Age	DRI (mg/d)	High PTH and normal phosphorus[a]	High PTH and high phosphorus[b]
0–6 months	100	≤ 100	≤ 80
7–12 months	275	≤ 275	≤ 220
1–3 years	460	≤ 460	≤ 370
4–8 years	500	≤ 500	≤ 400
9–18 years	1250	≤ 1250	≤ 1000

[a] *≤ 100% of the DRI.*
[b] *≤ 80% of the DRI.*
DRI, Dietary reference intake; *PTH*, parathyroid hormone.
Adapted and reproduced from Health Canada. Dietary reference intakes, http://www.hc-sc.gc.ca/fn-an/alt_formats/hpfb-dgpsa/pdf/nutrition/dri_tables-eng.pdf with permission from the Minister of Health, Health Canada 2020, © All rights reserved.

TABLE 34.9 Recommended supplementation for vitamin D deficiency/insufficiency in children with chronic kidney disease (CKD) [148].

Serum 25(OH)D (ng/mL)	Definition	Ergocalciferol (vitamin D2) or cholecalciferol (vitamin D3) dosing	Duration (months)
<5	Severe vitamin D deficiency	8000 IU/d orally or enterally × 4 wk or (50,000 IU/wk × 4 wk); then 4000 IU/d or (50,000 IU twice per mo for 2 mo) × 2 mo	3
5–15	Mild vitamin D deficiency	4000 IU/d orally or enterally × 12 wk or (50,000 IU every other wk, for 12 wk)	3
16–30	Vitamin D insufficiency	2000 IU daily or (50,000 IU every 4 wk)	3

[159,160]. It is important to note that some infants may require phosphorus supplementation in the form of sodium phosphate (Neutra-Phos) because of their higher physiological needs, as mentioned previously. Most other patients with CKD require oral intestinal phosphate binders to control hyperphosphatemia. Phosphorus control can be difficult in vegetarians since for the same total quantity of dietary protein delivered, the phosphorus content is greater in protein derived from vegetable sources (average 20 mg of phosphorus per g of protein) versus animal protein (average 11 mg of phosphorus per g of protein). However, the bioavailability of phosphorus from plant-derived food is very low; therefore despite their higher specific phosphorus content, some plant sources of protein may actually result in a lower rate of phosphorus uptake per mass of protein than meat-based foods [30]. Whereas food labels rarely state the phosphorus content [157], chocolates, nuts, dried beans, and cola soft drinks are rich in phosphorus and should be avoided; nondairy creamers and certain frozen nondairy desserts may be used in place of milk and ice cream.

Vitamin D

Vitamin D plays an important role in the management of CKD-MBD and its deficiency is a risk factor for SHPT and decreased serum 1,25 $(OH)_2D$ levels. Ali et al. reported a 20%–75% prevalence of vitamin D deficiency ($25(OH)_2D < 15$ ng/mL) in children with CKD stages 1–5, with higher prevalence rates in Hispanics and African-Americans, likely due to increased melanin content in their skin [161]. The CKiD cohort study observed vitamin D deficiency (<20 ng/mL) in 28% of the 506 children at enrollment [162]. Those with $25(OH)_2D$ deficiency were more likely to be of nonwhite race, older with higher BMI *z*-scores, lower milk intake, not receiving vitamin D supplement, had more proteinuria and had higher FGF-23 levels [162]. While the total $25(OH)_2D$ and vitamin D–binding protein levels are lower in healthy black adults and black children when compared to white individuals, the bioavailable 25(OH)D levels are not different from white racial groups [163,164]. Current guidelines suggest checking serum $25(OH)_2D$ levels once every 6–12 months in children with CKD stages 2–5 [30,165]. If the serum level of $25(OH)_2D$ is <30 ng/mL, supplementation with vitamin D_2 (ergocalciferol) or vitamin D_3 (cholecalciferol) is suggested, with the specific dosing regimen dependent on the severity of the deficiency (Table 34.9). Cholecalciferol appears to have higher bioefficacy than ergocalciferol, although long-term comparative trials are lacking in humans [166,167]. During the repletion phase, serum levels of calcium and phosphorus should be measured 1 month following the initiation or a change in the dose of vitamin D and at least every 3 months thereafter. Once patients are replete with vitamin D, supplemental vitamin D should be continued and 25(OH)$_2$D levels checked yearly [30,148].

Acid–base and electrolytes

Acid–base status

Infants and children normally have a relatively larger endogenous hydrogen ion load (2–3 mEq/kg) than do adults (1 mEq/kg); in turn, metabolic acidosis is a common manifestation of CKD in children and an important negative influence on growth through a number of growth factor specific mechanisms, including a reduction in thyroid hormone levels and blunting of the IGF response to GH [168]. Furthermore, studies performed in adults and children have shown that chronic acidosis is associated with increased oxidation of branched-chain amino acids, increased protein degradation [169], and decreased albumin synthesis [170]. Persistent acidosis also has detrimental effects on bone because it alters the normal accretion of hydroxyapatite into bone matrix and causes bone demineralization as bone buffers are increasingly used for neutralizing the excess acid load. Thus it is recommended that the serum bicarbonate level should be maintained at or above 22 mEq/L in children with CKD by supplementing with oral bicarbonate as needed [30].

Sodium

Sodium requirements in children with CKD are dependent on the underlying kidney disease and the degree of renal insufficiency. Children who have CKD as a result of obstructive uropathy or renal dysplasia are most often polyuric and may experience substantial urinary sodium losses despite advanced degrees of CKD. Sodium depletion adversely affects growth and nitrogen retention [171], and its intake supports the normal expansion of the ECF volume needed for muscle development and mineralization of bone [172]. Fine et al., demonstrated poor weight gain in animals deprived of salt with a resultant decreased extracellular volume, bone mass, and fat mass [173]. Parekh et al., reported the beneficial effect of a dilute, sodium supplemented (2–4 mEq sodium per 100 mL formula), high-volume (180–240/kg per 24 hours, depending on urine output) feeding regimen on the linear growth of 24 young children with severe polyuric CKD. The treated group of patients was able to maintain a nearly normal height SDS despite the presence of significantly impaired kidney function [174]. Therefore infants and children with polyuric salt-wasting forms of CKD who do not have their sodium and water losses corrected may experience vomiting, constipation, and significant growth retardation associated with chronic intravascular volume depletion and a negative sodium balance [174]. It is important to note that normal serum sodium levels do not rule out sodium depletion and the need for supplementation. Sodium supplementation can be given as chloride or bicarbonate, depending upon the patient's acid–base status.

In contrast, children with CKD resulting from a primary glomerular disease, or those who are oliguric or anuric, typically require a sodium and fluid restriction to minimize fluid gain, edema formation, and hypertension. The prescribed fluid intake is usually a fraction of the calculated maintenance volume adjusted for the degree of oliguria. According to the most recent 2005 Dietary Guidelines, the sodium intake for children older than 2 years should be restricted to <1500 mg (65 mmol) [175], which corresponds to sodium intake of 1–2 mmol/kg per day for those younger than 2 years. These patients should be advised to avoid processed foods and snacks from fast-food restaurants as a substantial amount of sodium can come from salt added during food processing. In support of the recognized association between fast foods and salt intake, a cross-sectional study of dietary intake in the CKiD cohort revealed that the dietary sodium intake increased with age and exceeded the recommended maximum intake in all age-groups [97]; the median sodium intake was 83 mg (3.6 mmol)/kg per day [176]. Fast foods were the largest single source of sodium, contributing 9.4% of the total intake [176]. When stratified by age-group, cheese (10%) was the top contributor to sodium intake in children aged 2–5 years, while fast foods were the main source of sodium for children aged 6–13 (8.8%) and 14–18 (10.2%) years [176].

Infants receiving PD are particularly predisposed to substantial sodium losses, even when anuric. High ultrafiltration requirements per kilogram of body weight result in the removal of significant amounts of sodium chloride. These losses are not adequately replaced through the low sodium content of breast milk (160 mg/L or 7 mmol/L) or standard commercial infant formulas (160–185 mg/L or 7–8 mmol/L) [177]. Therefore infants on PD are at risk of developing hyponatremia that can result in cerebral edema and blindness and must be maintained in neutral sodium balance. Sodium supplementation should be individualized based on clinical symptoms, including hypotension, hyponatremia, and/or abnormal serum chloride levels.

Potassium

Potassium homeostasis in children with CKD is usually unaffected until the GFR falls to <10% of normal. However, children with renal dysplasia, postobstructive kidney damage, severe reflux nephropathy, and renal insufficiency secondary to interstitial nephritis often demonstrate renal tubular resistance to aldosterone and may manifest hyperkalemia, even when their GFR is relatively well preserved. The hyperkalemia experienced by these children is exacerbated by volume contraction (and can be particularly common in salt losers) and the majority of the patients respond to salt and water repletion. In patients who are persistently hyperkalemic, dietary potassium intake should be limited. As potassium content is infrequently listed on food labels and cannot be tasted, a list of foods rich in potassium such as chocolates, French fries, potato chips, bananas, green leafy vegetables, dried fruits, and orange juice should be provided to patients and their families. Altering the methods of food preparation, such as soaking vegetables before cooking, helps decrease potassium content. Moderate-to-severe hyperkalemia may require treatment with a potassium binder such as sodium polystyrene sulfonate (SPS) (Kayexalate), patiromer (Veltassa), or sodium zirconium cyclosilicate (Lokelma). In contrast to SPS that exchanges sodium for potassium ions, and can also bind calcium and potentially result in hypocalcemia, patiromer exchanges calcium for potassium ions thus avoiding the provision of a sodium load and the possible inadvertent development of hypocalcemia. At present, patiromer has only been approved for usage in adults and pediatric trials are ongoing.

In the case of infants and young children being fed milk formula, the potassium content of the formula can be reduced by pretreating it with a potassium binder, SPS, or patiromer [178]. It is important to note that pretreatment of milk formula with SPS can reduce the calcium concentration by 8%–29%, and increase the sodium concentration by 86%–300% [179, personal communication VC]. On the other hand, pretreatment with patiromer has no impact on sodium concentration, while it increases calcium concentration by 19%–43% [personal communication VC]. Alternatively, special milk formulas such as Renastart (Vitaflo USA) or Renalcal (Nestle Health Sciences) that are low in potassium and can be used to minimize the exposure to dietary potassium (Table 34.10) [180].

In children undergoing HD, dietary potassium intake should be distributed throughout the day, as high serum concentrations of potassium can develop when a large quantity of potassium is ingested at one time, regardless of the total daily dietary content. On the other hand, some patients receiving PD may become hypokalemic due to potassium losses in the dialysate and will require potassium supplementation, as hypokalemia has been associated with an increased risk for the development of peritonitis. Finally, if constipated, the patient should be treated aggressively as significant quantities of potassium are eliminated through the gastrointestinal route in patients with CKD.

Vitamins and micronutrients

Vitamins and minerals are essential for normal growth and development and either a deficiency or an excess can prove harmful. Unfortunately, the vitamin and mineral needs of pediatric patients with CKD are not clearly defined (other than for Vitamin D), and the limited data that are available are derived from patients undergoing maintenance dialysis. Children with CKD are prone to develop vitamin deficiencies because of anorexia and dietary restrictions, while they are also at risk to develop toxic levels of vitamins when the renal clearance is significantly impaired.

All of the water-soluble vitamins except pyridoxine are eliminated by the kidneys and their clearance in patients with CKD is not known. However, most

TABLE 34.10 Milk and selected commercial formula nutrient content per 100 kcal.

Milk/formula	Calories (kcal/oz)	Volume (mL)	Protein (g)	Sodium (mg)	Potassium (mg)	Calcium (mg)	Phosphorus (mg)
Cow's milk	19	159	5.1	79	248	200	148
Human milk	20	150	1.5	25	75	46	20
Similac PM 60/40	20	148	2.2	24	80	56	28
Renastart	30	100	1.6	50	23	22	19
Renalcal	60	50	1.7	3	4	3	5
Nepro	54	56	4.5	59	59	59	40
Suplena	54	56	2.5	44	63	59	40

Conversion mg to mEq: sodium 23 mg = 1 mEq; potassium 39 mg = 1 mEq. Human milk electrolyte composition can vary with maternal diet. Renalcal is a calorically dense, minimized electrolyte formula that should not be used as the only source of complete feeding.

Adapted from Chadha V, Woloshuk RJ, Warady BA. Nutrition in pediatric kidney diseases. In: Mitch WE, Ikizler TA, editors. Handbook of nutrition and the kidney. 7th ed. Philadelphia, PA: Wolters Kluwer; 2018. p. 245–8.

water-soluble vitamins are lost during maintenance dialysis and, in turn, are routinely supplemented by special vitamin formulations that do not contain vitamin A and D, such as Nephronex (L Lorens Pharmaceuticals), Nephro-Vite (Allergan Inc.), and Dialyvite (Hillestad Pharmaceuticals Inc.). Studies conducted in the adult dialysis population have provided evidence of low blood concentrations of water-soluble vitamins and minerals because of inadequate intake, increased losses, and increased needs [181,182]. Deficiency of vitamin B_6 can result from poor dietary intake as well as impaired formation and/or increased clearance of pyridoxal phosphate in the dialysis fluid [183]. Vitamin B_{12} and folic acid, both of which are important for effective erythropoiesis, differ in their peritoneal clearance; while there can be significant losses of folic acid, only small quantities of vitamin B_{12} are lost by this route [184]. Accordingly, supplementation with 0.8- to 1.0-mg folic acid is routinely recommended, while the necessity of vitamin B_{12} supplementation remains unsettled. A higher dose of folic acid (2.5 mg/d) has been suggested for children with CKD and on dialysis, as supplemental folic acid has been shown to decrease the elevated homocysteine levels that is commonly seen in patients with renal failure and that is a potential risk factor for cardiovascular morbidity and mortality [185,186]. In contrast, serum thiamine and riboflavin levels have been reported to be normal in PD patients, with or without supplementation, in association with negligible losses during dialysis [187].

Supplementation with vitamin C is occasionally recommended because of the significant quantity that can be lost during PD [188]. It is important to recognize, however, that while adequate levels of vitamin C are necessary for the formation of collagen, an excessive intake of vitamin C in the dialysis population may result in elevated oxalate levels as an end product of vitamin C metabolism and lead to the development of significant vascular complications [189]. Accordingly, vitamin C intake should not exceed 100 mg/d. Vitamin K deficiency is likely in patients who receive frequent antibiotics and has been reported in a small number of adults [190]. Vitamin A levels are usually elevated in patients undergoing PD despite the lack of vitamin A in the vitamin supplement formulation. The elevated levels are a result of the loss of the kidneys normal ability to excrete vitamin A metabolites [191]. Since elevated levels of vitamin A can be associated with the development of hypercalcemia and complications related to a high calcium−phosphorus product, it is critically important to avoid the use of vitamin supplements that include vitamin A.

In children older than 6 years of age undergoing PD, vitamin supplementation has been associated with normal or greater than normal serum levels of the water-soluble vitamins [188]. However, no published studies have assessed the blood vitamin levels of children undergoing maintenance dialysis in the absence of the use of a vitamin supplement. As most infant milk formulas, including Similac PM 60/40 are fortified with both water- and fat-soluble vitamins, most infants with CKD/ESKD receive the DRI/RDA for all vitamins (including vitamin A) by dietary intake alone. Warady et al. [192] reported on the vitamin status of a group of seven infants undergoing PD; their main nutrient intake was infant milk formula (Similac PM 60/40) and they received a water-soluble vitamin supplement (Iberet; Abbott Laboratories, Abbott Park, IL). The combined dietary and supplement intake exceeded the RDA for the water-soluble vitamins in all but one patient who received only 79% of the RDA for vitamin B_6 because of inadequate formula intake. In all cases, the patient's serum concentrations of the water-soluble vitamins were comparable to or greater than the values reported in normal infants. In addition, the serum vitamin A levels were significantly greater than normal values, despite the lack of supplemental vitamin A.

Aluminum, copper, chromium, lead, strontium, tin, and silicon levels have all been noted to be elevated in patients with CKD, reflecting the fact that their clearance is dependent on an adequate GFR [193,194]. Other trace elements have not been well studied in children; however, zinc levels have been shown to be low in malnourished children and should be monitored and supplemented as necessary [193].

Based on the limited data referred to earlier, the current KDOQI Pediatric Nutrition Guidelines [30] recommend the intake of at least 100% of the DRI for thiamin (B_1), riboflavin (B_2), niacin (B_3), pantothenic acid (B_5), pyridoxine (B_6), biotin (B_8), cobalamin (B_{12}), ascorbic acid (C), retinol (A), α-tocopherol (E), vitamin K, folic acid, copper, and zinc for children with CKD stages 2−5, and those receiving maintenance dialysis. They suggest supplementation of vitamins and trace elements if dietary intake alone does not meet 100% of the DRI or if clinical evidence of a deficiency, possibly confirmed by low blood levels of the vitamin or trace element, is present [30]. As most infant milk formulas are fortified with both water- and fat-soluble vitamins, the majority of infants with CKD (and not yet on dialysis) receive the DRIs for all vitamins (including vitamin A) by dietary intake alone and do not require vitamin supplementation.

Carnitine

Carnitine is essential for normal mitochondrial function, fatty acid and energy metabolism, and cell membrane stability [195]. While essential for life, carnitine is a nonessential compound because it can be endogenously synthesized from lysine and methionine in liver, kidney, and brain [196]. However, most of the body's carnitine (approximately 75%) is derived from dietary intake, primarily from the consumption of meat. Carnitine is essentially found in two forms in the body, as free carnitine and as acylcarnitines (compounds in which carnitine is bound, by acyl-binding, to fatty acids of varying size) [197]. Normally, free and acylcarnitines are excreted in the urine in constant proportions so that the serum acyl/free carnitine ratio stays constant. A cross-sectional study in adults showed that the serum total (sum of free carnitine and acylcarnitines), free and acylcarnitine concentrations in the CKD patients were each not different from the values in healthy individuals [198]. In contrast, in patients receiving HD, the serum-free carnitine concentration was significantly lower and the serum acylcarnitine concentration was significantly greater as compared to healthy subjects; as a result the ratio of acylcarnitine to free carnitine, an index of abnormal carnitine metabolism, is dramatically increased in patients receiving HD [198]. Serum acylcarnitines increase in CKD and HD patients primarily because of impaired renal excretion. Serum-free carnitine, on the other hand, is not reduced in CKD but decreases in patients who receive HD because of increased removal during dialysis [198]. While not extensively studied in patients receiving PD, carnitine deficiency seems to be almost as common in these patients as in patients receiving HD. In a study of 34 PD patients matched (age, sex, and dialysis duration) with 34 HD patients, the prevalence of carnitine deficiency was 8.8% in the PD group and 17.7% in the HD group. There was no difference in the distribution of serum total, free, and acylcarnitine concentrations between the two groups [199]. In another study, 20 children ages 2–18 years receiving PD were found to have low plasma free and elevated acylcarnitine at baseline when compared to a healthy matched control group. After a 30-day period of oral carnitine supplementation (50 mg/kg per day), there was a significant increase in plasma levels of both free and acylcarnitine; however, no change was seen in the acylcarnitine to free carnitine ratio [200].

Carnitine deficiency can result in the development of anemia, cardiomyopathy, and muscle weakness [201]. However, most, but not all, of the few pediatric studies that have been conducted on the subject of carnitine deficiency in dialysis patients have provided evidence for an increase in the plasma carnitine level after carnitine supplementation with no associated change in any symptoms [202]. As such, there currently is insufficient evidence to support the routine use of carnitine in either the pediatric CKD or dialysis patient populations. However, a trial of supplemental carnitine may be indicated when all other causes for the symptoms in question have been excluded, carnitine deficiency has been confirmed, and the patient has been unresponsive to standard therapies [203]. Carnitine deficiency is determined by measurements of plasma free and total carnitine with an acyl:free carnitine ratio greater than 0.4 [i.e., (total − free carnitine) ÷ free carnitine] or a total serum carnitine value less than 40 μmol/L [201].

Nutrition management

A registered dietitian with experience in pediatric kidney diseases should play the central role in the dietary management of children with CKD/ESKD. In addition to possessing knowledge related to nutritional requirements, this person should also be skilled in the evaluation of physical growth, developmental assessment, and the educational and social needs of this special population. The dietitian must be able to establish a positive rapport with both the child and the primary caretakers to enhance compliance with the recommended nutritional regimen. The focus of the dietitian's treatment plan is determined by the patient's age. In the case of infants, the parents or primary caretaker who is responsible for feeding the child has the greatest interaction with the dietician; in contrast, adolescents must receive the majority of information directly, as they often eat independently. For children between these two extremes, both the parents and the child are typically involved in different aspects of the dietary management. It is noteworthy that the two most vulnerable groups of patients in terms of the risk for malnutrition are infants and adolescents. While infants are at special risk because of the frequent occurrence of anorexia and emesis, many adolescents have poor eating habits, as mentioned previously.

An individualized nutrition plan taking into account a variety of factors should be developed for each patient by the dietician in consultation with the physician, patient (when appropriate), and family, with clearly defined short- and long-term objectives. As cultural food preferences play an important role in the family's ability to adhere to dietary changes, dietary instructions should be tailored to help families modify, but not eliminate cultural food preferences. Background information on cultural diets and translated versions of renal diets and food lists are available for reference [204]. The plan should be modified as necessary according to changes in the child's nutritional status, kidney function, dialytic therapy, medication regimen, and psychosocial situation with particular attention paid to any concerns for food insecurity.

Dietary restrictions should be limited as much as possible with a goal of enhancing nutrient intake. Restrictions of nutrients should ideally be imposed only when there is a clear indication, rather than an anticipated need. It is also important to find substitutes for restricted foods so as to maintain an adequate caloric intake. A simple explanation of the role of the nutrient in the body, the rationale for the diet modification, and the desired outcomes to be achieved (e.g., normalization of biochemical parameter, specific amount of weight gain) is helpful in obtaining cooperation of the patient and caretakers, thereby increasing the likelihood of success. Adopting and maintaining changes in eating habits is also easier for a child if family members make similar changes, or at least avoid eating restricted foods in the child's presence. In addition, caregivers outside of the immediate family (e.g., grandparents, school staff, babysitters) should be aware of the diet restrictions and be asked to provide consistency of care in helping the child follow his/her diet. While the ideal goal is full compliance with the prescribed regimen, it is not always a realistic expectation and "partial compliance" is often acceptable. Being very rigid with the dietary prescription adds to parental stress and increases the risk for behavioral eating problems in the young child such as food refusal, gagging, and vomiting.

Oral supplementation

Infants with CKD requiring fluid restriction or those who have a poor oral intake may require a greater caloric density of their milk formula than the standard 20 kcal/oz. The increase in caloric density should not be achieved by concentrating the milk formula, as this approach will also increase the protein and mineral content. The provision of extra calories can be achieved by adding carbohydrate and/or fat modules to the formula. Glucose polymers such as Polycose (Abbott Nutrition) or SolCarb (Medica Nutrition) have a low osmolality and are generally the initial supplements added to infant formulas. Additional calories can be added in the form of corn oil. Oils containing medium-chain triglyceride are generally not necessary unless there is coexistent malabsorption. However, usage of corn and other oils as additives is not common as they do not mix well with formula and cause problems with tube feedings. Microlipid (Nestle Nutrition), a 50% fat emulsion from safflower oil with 4.5 kcal/mL, and Duocal (Nutricia North America), a fat and carbohydrate combo modular with 5 kcal/g of powder (59% calories from carbohydrate and 41% from fat), are common commercially available products for energy supplementation. The latter is not approved for infants younger than 1 year. Older infants may tolerate the addition of corn syrup or sugar, which are readily available and inexpensive. The quantity of both carbohydrate and fat modules can gradually be increased to raise the caloric density to as much as 60 kcal/oz [205]. It is important to wait at least 24 hours following each 2- to 4-kcal/oz incremental increase in concentration to enhance patient tolerance of the formula.

Nutritional therapy, irrespective of the route of administration or the caloric density of the formula, should provide a balance of calories from carbohydrate and unsaturated fats within the physiological ranges recommended as the Acceptable Macronutrient Distribution Ranges (AMDR) of the DRI. Recommended AMDR for children older than 4 years are 45%–65% from carbohydrate, 25%–35% from fat (polyunsaturated/saturated ratio of 1), and 10%–30% from protein; children younger than 3 years need a somewhat greater proportion of fat (30%–40%) in their diets to meet energy needs. An adequate amount of nonprotein calories should be provided for protein-sparing effects. It should, however, be noted that during the advanced stages of uremia, the protein-sparing effect of added fat calories may be inferior to the effect of added concentrated carbohydrate calories [38]. Unfortunately, children beyond infancy characteristically refuse the high-calorie carbohydrate supplements. For them, it is often easier to encourage common foods that have a high caloric content, but a relatively low mineral and protein content. Powdered fruit drinks, frozen fruit-flavored desserts, candy, jelly, honey, and other concentrated sweets can be used for this purpose. However, the altered taste acuity associated with uremia may limit the acceptability of these foods. In addition, one may need to avoid high carbohydrate foods in the presence of hypertriglyceridemia. Under these circumstances, unsaturated fats may be the preferred choice of high-calorie food sources. Children and adolescents should also be encouraged to use margarine on popcorn, bread, vegetables, rice, and noodles for added calories.

A variety of calorie-dense (1.8 kcal/mL) preparations such as Nepro and Suplena (Abbott Nutrition) have been formulated specifically for renal patients and are commercially available. Suplena has a lower protein content than Nepro (30 vs 70 g/L) and is preferable for predialysis patients. These preparations are characterized by a low renal osmolar load and a low vitamin A and D content. Although initially produced for patients older than 10 years, they have been successfully used in children as young as 3 years; however, it is advisable to dilute them to half to two-third strength when used in young children. Hobbs et al. reported the successful use of these adult renal formulas in seven hyperkalemic infants with improved growth and normalization of the serum potassium level [206].

In contrast to energy intake, the protein requirements of children with CKD are usually met by voluntary, unsupplemented consumption. A recently published CKiD experience revealed that the median DPI of children with CKD exceeded recommended levels in all age-groups, particularly among younger subjects [97]. However, if on occasion the protein intake is insufficient due to concomitant phosphorus restriction in a patient with severely impaired kidney function, the protein module, Beneprotein (Nestle Nutrition), a whey protein concentrate, can be added to the formula to increase the protein content. As much as 1 g of Beneprotein, which is equivalent to 0.86 g protein, can be added to each ounce of formula. Semisynthetic diets supplemented with either amino or keto forms of essential amino acid have also been tried to ensure an adequate protein intake. However, the lack of sufficient data in children precludes making any firm recommendation regarding their possible clinical application.

Enteral nutritional support

Aggressive enteral feeding should be considered if the nutritional intake by the oral route is suboptimal despite all attempts at oral supplementation. The use of enteral support has resulted in maintenance or improvement of SD scores for weight and/or height in infants and young children with moderate-to-severe CKD and those undergoing maintenance dialysis [4,12,19,101,207,208]. In fact, several investigators, including Kari et al. [96], have advocated early enteral feeding at the first sign of growth failure during infancy.

Nasogastric (NG) tubes, [207,208], gastrostomy catheters [209], gastrostomy buttons [210,211], and gastrojejunostomy tubes [212] have all been used to provide supplemental enteral feeding to children with kidney disease with encouraging results. The feeding can be given as an intermittent bolus, or more commonly by continuous infusion during the night. Continuous overnight feeds are generally preferred to allow time during the day for regular oral intake. Historically, the NG tube was used most frequently in infants and young children, as it is easily inserted and is generally well tolerated [208]. Ellis et al. reported the usage of an NG tube by 78% and 68% of children who initiated dialysis at <3 months and 3–20 months of age, respectively [213]. However, this route of therapy is often complicated by recurrent emesis and the need for frequent tube replacement, in addition to the risk of pulmonary aspiration, nasoseptal erosion, and psychological distress of the caretaker because of the cosmetic appearance. Persistent emesis can be addressed by slowing the rate of formula delivery and by the addition of antiemetic agents such as metoclopramide or domperidone. Additionally, whey predominant formulas can be used as they have been shown to stimulate gastric emptying [214,215].

The gastrostomy tube or button has more recently been used as the enteral route of choice by many clinicians and has the cosmetic advantage of being hidden beneath clothing. Once placed, it can be used within several days. Many, but not all, clinicians recommend that the patient should be investigated for gastroesophageal reflux prior to undertaking gastrostomy placement so that a Nissen fundoplication can be carried out at the same sitting, if required. The reported complications of gastrostomy tubes/buttons include exit-site infection, leakage, obstruction, gastrocutaneous fistula, and peritonitis in patients receiving PD [216,217]. Peritonitis is potentially the most serious complication and is a likely factor inhibiting the more widespread adoption of gastrostomy as opposed to NG feeding in the PD population [218]. In the SCOPE (Standardizing Care to Improve Outcomes in Pediatric ESRD) collaborative analysis, patients with a gastrostomy had a higher incidence of peritonitis on univariate analysis [219]. Warady et al. reported that 11 (24%) of 45 episodes of fungal peritonitis were associated with the presence of a gastrostomy tube or button, but there was no statistically significant correlation between the presence of a gastrostomy and the development of fungal peritonitis [220]. This finding was recently confirmed by a subsequent SCOPE collaborative report on 41 episodes of fungal peritonitis [221]. To decrease the risk of peritonitis, the gastrostomy should be placed either before or simultaneously during PD catheter placement, accompanied by antibiotic and antifungal prophylaxis [30,222]. In addition, it may be better to avoid combining gastrostomy placement and PD catheter placement in a severely malnourished patient until the nutritional status and general immunity of the patient can be improved by other means, such as NG tube feeds [217].

Rees et al. [101], in a study of the IPPN, demonstrated the effectiveness of NG tube and gastrostomy feeding in improving the nutritional status of young (<2 years) children receiving chronic PD. The authors also observed that the use of gastrostomy in contrast to NG tube was associated with better growth, believed to be due to decreased vomiting seen with gastrostomy feedings. However, a recent IPPN report also revealed marked global variation in feeding strategies and the complex relationship between enteral feeding and growth. According to the report, gastrostomy usage was more common in North America, Western Europe, Korea, and New Zealand and was associated with the development of obesity [12]. BMI SDS at PD initiation was associated positively with eGFR and gastrostomy feeding prior to PD initiation. Finally and surprisingly, the authors also noted that obese, but not underweight, patients were significantly shorter than patients with a normal nutritional status at the initiation of PD [12]. This finding, and similar observations made previously, confirms that correction of growth failure may not always be achievable by just increasing the caloric intake.

A common and serious complication of using any form of enteral tube feeding is a prolonged and potentially difficult transition from tube to oral feeding [223,224]. Regular nonnutritive sucking and repetitive oral stimulation are recommended for all tube-fed infants. A multidisciplinary feeding team consisting of a dietitian, occupational therapist, and behavioral psychologist can help facilitate the transition from tube to oral feeding.

Alternative routes of nutritional support

The substitution of amino acids for dextrose in the PD fluid and the provision of parenteral nutrition during HD sessions (intradialytic parenteral nutrition; IDPN) are two additional aggressive approaches to nutritional supplementation that have had limited pediatric application. Intraperitoneal nutrition has been evaluated in only a small number of children receiving PD and for a limited period of time [116,117,225]. The quantity of amino acids absorbed from the dialysate routinely exceeded the protein lost in the dialysate. Very little experience with IDPN has been reported in the pediatric population. A short-term study of 10 chronic HD patients, ages 10–18 years, conducted in the Netherlands documented weight gain in 9 patients with no significant change in the plasma amino acid profile [226]. Similarly, Goldstein et al. demonstrated a reversal of weight loss and initiation of weight gain within 6 weeks of IDPN initiation in 3 malnourished adolescents undergoing HD [227]. Future studies may prove these routes of nutritional supplementation to be valuable adjuncts to the oral and enteral routes of therapy.

Finally, children receiving three times a week HD have to endure dietary restrictions that can be removed with daily intensified HD. Fischbach et al. showed significant catch-up growth (mean growth velocity increased from 3.8 ± 1.1 cm/year at baseline to 14.3 ± 3.8 cm/year during the first year) with intensified hemodiafiltration and continued GH therapy in 15 children with a mean age of 8.25 years [228].

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CHAPTER

35

Metabolic management and nutritional support in acute kidney injury

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Introduction

Acute kidney injury (AKI) is a clinical syndrome that can evolve from many different etiologies and is associated with a broad spectrum of severe short- and long-term consequences [1]. The pattern of renal dysfunction ranges from simply functional, in many instances volume responsive impairment, to gross tubular injury with a complete shutdown of exocrine renal function with the necessity of extracorporeal organ support [2].

Critical for the understanding of the manifold presentations of AKI is the fact that when the complex functions of the kidney, the main regulatory organ of the body for maintaining fluid compartments and electrolyte-homeostasis (milieu intérieur) and its multiple endocrine, metabolic, and immunologic tasks are impaired, practically all physiologic pathways and organ functions in the body are affected. Actually, AKI in its more severe forms presents a "pan-metabolic, pan-endocrine, pan-organ syndrome."

Consequences of AKI thus not only include direct and immediate effects such as an impairment of fluid, electrolyte, and acid–base homeostasis, but also a broad range of endocrine, metabolic, and immunologic complications [3]. Clinically important is the fact that an impairment of renal function causes an augmentation of inflammation, by which secondary damage to other organs (distant organ injury) is induced that, in a vicious cycle, augments renal injury [4,5]. A patient does not (only) die "in AKI"—as was previously often assumed—but also "from" AKI.

AKI, however, is also associated with severe long-term consequences and can exert a dramatic impact on the future life of the patient who survives an AKI episode. This includes a reduced life expectancy, an impaired quality of life, an increased risk of developing chronic kidney disease (CKD), cardiovascular disease, hypertension and immunological disorders with an increased risk of developing infections, neoplasia, and end-stage renal failure [1,3].

Because of these often dramatic consequences of loss of renal function, prevention of AKI is of utmost importance, and if renal dysfunction has occurred, to reduce the risk of progression of chronic renal disease and when possible to reverse renal functional loss [6]. Moreover, when AKI has occurred, the untoward consequences must be minimized as far as possible to enable and promote recovery of renal function. Within this context the metabolic management of the patients, in addition to nutritional therapy, includes the management of volume status and electrolyte and acid–base balance.

AKI is defined and classified into three stages of severity according to the criteria proposed by the "Kidney Disease: Improving Global Outcomes" initiative (Table 35.1) [2]. Especially important with respect to the prevention, early diagnosis and therapy is the fact that even small changes in renal function (as reflected by minimal increases in serum creatinine of >0.3 mg/dL) have prognostic relevance for the further course of disease and is designated as a "risk stage," that is, AKI-1. The more severe stages of renal dysfunction are designated as "injury" (AKI-2) and "failure" (AKI-3). If renal replacement is required, it is classified as AKI-3D (Table 35.1). When the pathophysiologic process is ongoing, the syndrome has recently been termed acute kidney disease [7].

The three stages of AKI profoundly differ not only in the clinical presentation but also in the metabolic environment and nutrient requirements of the patient.

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TABLE 35.1 Staging of acute kidney injury by Kidney Disease: Improving Global Outcomes Guidelines.

Stage	Serum creatinine	Urine output
1	1.5–1.9 times baseline OR ≥ 0.3 mg/dL (≥ 26.5 mmol/L) increase within 48 h	<0.5 mL/kg/h for 6–12 h
2	2.0–2.9 times baseline	<0.5 mL/kg/h for ≥ 12 h
3	3.0 times baseline OR Increase in serum creatinine to ≥ 4.0 mg/dL (≥ 353.6 mmol/L) OR Initiation of renal replacement therapy OR In patients <18 years, decrease in estimated GFR to <35 mL/min/1.73 m^2	<0.3 mL/kg/h for ≥ 24 h OR Anuria for ≥ 12 h

GFR, Glomerular filtration rate.

Adapted from the Kidney Disease: Improving Global Outcomes (KDIGO) Acute Kidney Injury Work Group. KDIGO clinical practice guideline for acute kidney injury. Kidney Int Suppl 2012;2(1):1–138.

Thus the metabolic management and nutrition support must be adapted to these different stages of AKI. Moreover, because of the broad pattern of etiologies and clinical presentations of AKI patients and the dynamic, often fluctuating course of their diseases, the therapeutic regimens, and especially the metabolic management and nutrition support for these patients, must be individualized for each patient and at each time point during the patient's clinical course.

A further point that should be considered is the fact that the epidemiology and clinical presentation of AKI may fundamentally differ between community acquired conditions (often in the context of preexisting chronic systemic disease), hospital-acquired AKI (mostly more complex causes) and intensive care unit (ICU) acquired AKI with the latter often being caused by severe infections/septicemia and presenting as a part of multiple organ dysfunction syndrome (MODS) [8–10]. Nevertheless, many patients with AKI are not critically ill and are cared for on open wards. These patients need a stage-specific approach to their nutritional management.

As a consequence of this clinical heterogeneity nutritional support of AKI patients is one of the most challenging situations in clinical nutrition. However, although AKI is a commonly occurring disorder, there very few systematic studies concerning its nutritional management. Thus most recommendations are not based on high-quality randomized controlled trials (RCTs), but must largely rely on expert opinion.

The most recent recommendations from international nutrition societies (ASPEN, ESPEN) on nutrition support in critically ill patients address only single points in nutritional support for patients with AKI [11,12]. Specific guidelines for patients with AKI issued by ASPEN are mostly outdated and are currently undergoing revision, ESPEN recently has published revised recommendations [13,14].

In this chapter a stage-specific approach to the metabolic management for prevention, therapy, and nutrition support of patients with acute renal dysfunction is summarized and a more holistic metabolic approach beyond classical nutritional interventions is proposed.

Metabolic management in the prevention of AKI and the therapy of AKI/risk stage AKI-1

In consideration of the severe short- and long-term consequences of AKI, the major impact of AKI on morbidity and mortality, the possibility of continuing risk of renal injury, and the potential for permanent loss of renal function, the restoration of renal function is of major clinical importance [6]. To restore renal function, it is important to note that many metabolic and nutritional interventions may have a previously mostly unrecognized role.

There is no effective pharmacologic therapy for AKI [6]. Therefore the general management of the patient and the optimization of hemodynamics, the volume state, respiratory function, the metabolic balance, including electrolyte-homeostasis and acid–base equilibrium and the avoidance of nephrotoxic medicines, are the most important means to preserve microcirculation and to preserve or restore kidney function [2] (Table 35.2).

Preconditioning

Preconditioning encompasses strategies, which applied before an injurious event (such as elective surgery and contrast media application) enhance the organ tolerance to subsequent insults. Most extensively

TABLE 35.2 Metabolic management in the prevention of acute kidney injury (AKI) and therapy of AKI-1 (risk stage).

- Preconditioning (?)
- Volume therapy
  - Infusion solutions: chloride reduced, no artificial colloids
  - Avoidance of hypovolemia and hypervolemia
- Prevention/correction of electrolyte imbalances
  - Potassium, phosphate, magnesium
- Prevention/correction of deficiency states
  - Thiamine, vitamins B6 and C, folate?
- Prevention/correction of metabolic acidosis?
- Prevention/correction of hyperglycemia
- Early start of (whenever possible) oral or enteral nutrition
- Avoidance of hypercaloric nutrition in the early phases
- Higher protein-/amino acid intake in the early phases?

investigated was remote ischemic preconditioning in the prevention of AKI. Results from RCTs and subsequent metaanalyses unfortunately were quite conflicting [15].

A further type of preconditioning is dietary restriction (DR), which extends life span and increases resistance to multiple forms of stress. Animal experiments have shown that with even brief periods of DR both calorie and protein restriction (PR) can prevent renal injury [16,17]. In a first RCT, patients scheduled for heart surgery were either subjected to caloric restriction (60% of calculated requirements) or received an ad libitum control diet for 7 days before surgery [18]. the primary endpoint, the rise in serum creatinine within 24 hours was negative; however, the further rise within 48 hours was lower ($P < .03$). There were no other differences in clinical relevant endpoints between the two groups. Unfortunately, the absolute difference in caloric intake was not assessed.

Whether a potential protective effect of DR for preserving renal function is related to calorie restriction of rather to PR remains to be shown. In any instance, DR is more of theoretical interest, rather of limited clinical relevance, which could potentially at best be an intervention for a rather small group of well nourished patients before hospital admission for elective surgery and not for patients at risk for AKI within the hospital (see next).

Volume management

Obviously, volume management plays a central role in the prevention of AKI. However, not only hypovolemia but also hypervolemia is of importance in deterioration of renal function [19].

Infusion solutions for prevention of AKI: The type of infusion solutions has gained much interest in recent years. It has become clear that artificial colloids used for volume resuscitation can exert a nephrotoxic effect by inducing nephrosis-like lesions in the kidney, including tubular swelling and necrosis, by intracellular and intratubular accumulation of colloids. Several countries as well as the European Union have released warnings and restrictions for the use of artificial colloids in ICU patients. Whether the physiological and natural colloid human albumin exerts advantages in this regard is the subject of much debate and remains unsettled [20].

Thus in prevention and management of early stages of AKI, crystalloid infusion solutions are preferable. However, from a metabolic point of view, the type of crystalloid is relevant in respect to prevention of AKI. Chloride was shown to be a selective vasoconstrictor of renal vessels [21,22]. Normal saline, as compared to a chloride-reduced "balanced" infusion solution, reduced renal cortical perfusion in healthy adults [23]. Normal saline as the main infusion solution may increase renal injury both in noncritically ill and critically ill patients [24,25]. Thus a lower chloride infusion regime by using balanced electrolyte solutions, such as lactated Ringer's, is preferable for patients at risk of AKI [6].

Electrolyte-homeostasis and acid–base balance

Until recently, little attention has been given to the importance of maintaining electrolyte balance in the prevention of AKI. In experimental studies, deficiency states of magnesium, potassium, and phosphate each can augment renal injury [26]. Avoidance of magnesium deficiency may prevent the development of AKI [27]. Thus deficiencies of these electrolytes should be prevented and/or corrected.

Acidosis: There is a decade-old discussion on the potential of intravenous bicarbonate to prevent AKI. This type of intervention should be distinguished from alkalization therapy for metabolic acidosis. In animal experiments, acidosis aggravates renal injury after ischemia–reperfusion injury [28].

Interest in this matter was stimulated by a large RCT, where the correction of severe metabolic acidosis ($pH < 7.2$) in critically ill patients using bicarbonate infusions reduced the risk of renal replacement therapy (RRT)-dependent AKI-3D and improved prognosis in patients with AKI-2−3 [29]. Whether this protective effect is mediated by the lower frequency of hyperkalemia as an indication for RRT or whether alkalization per se may exert a direct nephroprotective potential remains to be shown. Given the fact that even mild acidosis in humans is associated with such adverse events as negative protein balance, it could be argued that even mild acidemia probably should be avoided in patients with or at increased risk for kidney injury [30].

Hyperglycemia

Hyperglycemia interferes with endothelial structure and functions, compromises renal autoregulation, promotes oxidative stress and inflammation, and can aggravate renal injury. These detrimental effects of hyperglycemia on the kidney have been delineated in many animal experiments [31]. Clinical studies in various groups of acutely ill patients indicate that stress-induced hyperglycemia is associated with an increased risk of kidney damage and the development of AKI [32]. Hyperglycemia certainly is a cofactor that increases the susceptibility to renal injury.

In a secondary analysis of two larger RCTs on glucose management in critically ill patients, tight glucose control was associated with a 40% lowered incidence of AKI and a reduced need for RRT [33]. Although a nephroprotective effect of lowering blood glucose concentrations has not been uniformly confirmed in all studies, there is agreement that glucose concentrations should be kept below 180 mg/dL in any acutely ill patient [11,12]. Accordingly, correction of hyperglycemia is included in all recommendations for prevention and conservative therapy of AKI and constitutes a component of all treatment guidelines for the prevention of AKI [2,34]. Since blood glucose concentrations fluctuate in hospitalized patients, some institutions aim for a blood glucose target of 150 mg/dL to reliably maintain the glucose level below 180 mg/dL.

Endocrine/metabolic interventions

Various endocrine interventions to prevent the development of AKI and/or hasten renal regeneration have been evaluated. In experimental models of AKI, interventions such as thyroxine, recombinant human growth hormone (rHGH), epidermal growth factor (EGF), insulin-like growth factor (IGF)-1, hepatocyte growth factor, or erythropoietin (EPO) have been shown to prevent renal injury or to accelerate tubular regeneration.

In none of the (mostly older) clinical studies have these beneficial effects been confirmed. In a small pilot study, infusion of rHGH reduced protein catabolism and improved nitrogen balance [35]. However, administration of rHGH was associated with increased mortality of critically ill patients, many of whom had AKI [36]. A multicenter study of administering IGF-1 to AKI patients was terminated early because of the lack of benefit [37]. Administration of triiodothyronine that could potentially upregulate the EGF receptor expression was not only ineffective in patients with AKI but actually increased mortality [38]. Finally, in a large multicenter RCT in AKI patients, EPO failed to exert any clinical benefit [39].

In animal experiments and in some clinical investigations (contrast media exposure, perioperative patients), several nutritional molecules, mainly antioxidants, such as vitamin C, vitamin E, selenium, zinc or resveratrol, have been shown to protect against renal injury [40,41]. However, these beneficial effects have not been confirmed in patients in large RCTs, and none of these interventions has become standard clinical care.

Nutrition in the prevention of AKI and therapy of AKI-1

Nutrition therapy (oral/enteral/parenteral) in prevention and in the early stage of AKI-1 is not fundamentally different from that in other patient groups [11,12]. Nevertheless, in respect to preservation of renal function, some points should be considered.

Initiation and route of nutrition support

Whenever possible, oral or enteral nutrition should be used. In experiments in animals, enteral nutrition increased renal perfusion and improved renal function [42]. As in other acutely ill patients, nutrition support should be started early, but at a low rate and the nutritional intake should be increased slowly according to the individual tolerance of the patient [43].

In a large RCT comparing permissive underfeeding (but a comparable protein intake) with full caloric nutrition in critically ill patients, subjects receiving full nutrition from the beginning of their nutritional support had a higher rate of AKI requiring RRT [44]. This was confirmed in subsequent studies. Hence, it is important to note that an early high energy intake may increase the risk of developing AKI [45].

A current controversy relates to the question of the optimal protein/amino acid intake in these patient groups and whether a high intake may be protective by activating renal reserve capacity (i.e., the percentage increase in renal function in a postabsorptive patient after taking a defined protein load) [46].

In patients with cirrhosis of the liver, an amino acid infusion increased renal plasma flow by 32% and glomerular filtration rate (GFR) by 22% [47]. A small pilot study in critically ill patients had suggested that a higher amino acid intake (about 2 g/kg/d) lowers serum creatinine, increased diuresis and lowers the need for diuretics [48]. A large randomized controlled study using an intravenous amino acid infusion of 1 g/kg/d in addition to the protein intake associated with nutrition support (about 1 g/kg/d) improved renal function during the first 4 days but had no effects on "hard" endpoints, such as implementation of RRT, length of hospital stay or survival [49].

In a post hoc analysis of this study the increased amino acid intake protected against the development of AKI and improved outcome in those patients who did not show renal injury at the start of therapy [50]. In a recent study, cardiac surgery patients received an amino acid infusion immediately after induction of anesthesia [51]. Duration of AKI was shortened, estimated GFR and urine output were significantly improved after surgery, but again, the more relevant clinical endpoints were not affected. Certainly, more evidence is needed from RCTs, and for the time being no definite recommendations can be given concerning administration of larger amounts of protein or amino acids in these patient groups for the prevention of AKI.

In various older experiments in animals, it was suggested that some amino acids, such as arginine, glutamine, or taurine, may exert specific nephroprotective properties beyond just providing substrates for protein or peptide synthesis, nitrogen and carbon for urea synthesis, and stimulation of renal reserve capacity. Arginine (and also glutamine by improving renal arginine metabolism) has been of particular interest. Arginine, by producing nitric oxide, might potentially preserve renal perfusion and tubular function during either nephrotoxic or ischemic injury, whereas inhibitors of nitric oxide synthase might exert an opposite effect [52]. However, evidence from clinical investigations is scarce and controversial, and none of these approaches is currently used clinically [53].

Fish oil–containing lipid emulsion may reduce the risk of renal injury in animal models of AKI [54]. However, convincing clinical evidence concerning nephroprotective effects of fish oil in AKI is lacking.

Preexisting deficiency states (electrolytes, micronutrients, such as thiamine) should be corrected to avoid untoward side effects of malnutrition and the development of a refeeding syndrome [55]. In a secondary analysis of an RCT, thiamine supplementation in critically ill patients reduced the incidence of AKI [56].

Maintaining metabolic balance is also important in noncritically ill patients, and standard oral nutritional supplements (ONS) can be used if required.

Nutrition solutions

In these patient groups with this low stage of AKI, no specific nutritional preparations should be used for enteral or parenteral nutrition (PN).

Metabolic support in AKI stages 2 and 3 without the need for renal replacement therapy

The more severe stages of a renal injury AKI-2–3 in patients who do not need RRT are extremely frequent. By definition, patients with these AKI stages are clinically unstable, and careful management is crucial. There are almost no systematic studies concerning the metabolic management and nutritional support in these stages of AKI. The general management of these patients with AKI is as delineated previously and must be a leading goal of therapy (Table 35.1). Even in these stages of AKI, a primary goal must be the stabilization or improvement of renal function; the measures to attain this aim are not fundamentally different from those used in the management of other clinically unstable acutely ill patients.

In these stages of AKI, maintaining a balanced metabolic environment (with regard to electrolytes, glucose, triglycerides, acid–base balance) also must be a primary goal of therapy. Hyperglycemia again is a risk factor for AKI. Periprocedural hyperglycemia increases the risk of developing AKI or of intensifying the severity of AKI during surgery, ischemia, or exposure to nephrotoxins [57,58]. With regard to acid–base balance, in a large cohort analysis, alkalization therapy in patients with sepsis and severe metabolic acidosis ($pH < 7.2$) was associated with improved survival in patients with AKI-2–3 [59].

Nutrition support

Patients with AKI-2–3 commonly are unstable and have high variability in their clinical course; their renal injury may be stabilized, improve or progress to AKI requiring RRT. In these stages, it is of utmost importance to adapt the metabolic management and nutritional support to the individual condition of each patient; the modern postulate of "personalized care" is especially relevant for these phases of AKI.

It has been a widely held opinion that at the risk of sacrificing renal function in these stages of AKI, RRT should be started early to enable adequate nutritional support. In general, such a view can no longer be maintained. Each type of RRT is associated with a specific pattern of complications that are often serious; patients on RRT have increased mortality. Thus RRT should only be used when it is necessary [60]. Patients who have a chance for stabilization or even improvement of renal function should be identified, and nutritional therapy must be adapted to avoid progression of renal insufficiency or development of uremic symptoms.

Initiation and route of nutrition support

For more stable patients who are not hypercatabolic patients (AKI-2 and early AKI-3) and who are cared for on an open ward, oral nutrition should be started at a low rate and adapted slowly according to the individual tolerance of the patient. Of special importance, protein intake should be initially low (0.3–0.4 g/kg/d) and increased slowly, if at all, according to SUN (serum urea nitrogen). Some experts recommend using supplements of essential amino acids or keto-acids during this phase of AKI. Again, metabolic balance (electrolytes, acid–base, micronutrients, avoidance of hyperglycemia) must be carefully observed and managed in these patients.

In critically ill, unstable patients, nutritional support should be started early, but at a low rate and, again, should be increased slowly according to the individual tolerance of the patient.

Energy intake: In unstable stages of AKI-2–3 patients who do not need RRT, full "normocaloric" nutrition should not be pursued or forced. Rather, in analogy to other critically ill patients, a mild "permissive" hypoalimentation should be aimed at where according to the tolerance of the patient about 50%–70% of calculated or measured energy expenditure should be provided [11]. An exaggerated energy intake can induce a further deterioration of renal function in these AKI stages [45].

Glucose intake: As was shown many years ago, glucose infusion during ongoing renal injury can aggravate renal tubular damage [61]. In contrast, a glucose-reduced nutritional regimen may decrease the risk of AKI in critically ill patients [62].

Protein intake: Many years ago, animal experiments demonstrated that a high amino acid intake during the injury stage of AKI can aggravate renal damage and uremic toxicity (amino acid paradox) [63]. In agreement the abovementioned RCT that demonstrated a positive effect of a high amino acid infusion on renal function and prognosis in patients with no or minimal renal injury found negative consequences of a high intake in patients with more advanced renal impairment [50].

A secondary analysis of a large RCT comparing the effect of early versus late PN in intensive care patients revealed that an early high amino acid intake was associated with an increased need for RRT. Most of the additional amino acids provided did not enhance anabolism but increased urea generation [64]. Thus a high protein intake in this phase of AKI may increase renal injury and enhance the need for RRT.

In a large multicenter RCT evaluating the effects of a combination of enteral and parenteral glutamine in critically ill patients, mortality was increased during glutamine supplementation in patients who had kidney injury at their enrollment into the study [65].

The intake of protein/amino acids in AKI patients must be monitored regularly by measuring serum or plasma urea concentrations and be modified accordingly. Usually, the protein intake should not be higher than 0.6–1.0 g/kg/d [14]. Neither intravenous nor enteral glutamine should be provided in patients with AKI-2–3 [11].

Nutrition solutions: International societies do not recommend the use of specific "nephro" diets (for details vide infra) but rather standard solutions for both enteral and PN in AKI-2–3 patients.

Amino acid solutions adapted to uremic metabolism and with a high content of anabolic essential and conditionally essential amino acids are available in some countries [66]. Theoretical advantages, such as a normalization of plasma amino acid pattern, a reduction of urea formation, and improved protein synthesis, could not be confirmed in larger studies using relevant clinical endpoints.

For ONS/enteral nutrition, there are specific commercially available diets designed for predialysis CKD patients (CKD-3–5) (see next). These diets are low in electrolytes (sodium, potassium, phosphate), have a low-protein content, and potentially might display some metabolic advantages in more stable AKI-2–3 patients, but systematic studies are not available.

Metabolic management and nutritional support in patients with AKI-3 (and CKD-5) requiring renal replacement therapy (AKI-3D)

The traditional indication for nutritional support in AKI involves more clinically stable patients with established AKI-3 who require RRT (AKI-3D). A very complex metabolic environment is present in these patients, and both the impact by AKI per se and of RRT on their metabolism and nutrient balances should be considered when designing a nutritional prescription.

Metabolic alterations specifically induced by acute renal dysfunction

AKI is a syndrome, a complication that occurs with various etiologies and in heterogeneous clinical situations. Hence, the metabolism of AKI patients is affected not only by renal dysfunction but also by the type and intensity of RRT, the underlying disease process, associated comorbidities, dysfunctions of other organs, and such complications as infections.

There are inherent problems with the mostly older studies on metabolism in AKI. Animal experiments are hardly representative of the more prolonged clinical cases of AKI, particularly in cases treated with RRT. Moreover, unlike with humans with AKI, in animal studies of AKI, often the only clinical disorders in the animals were AKI and the technique used to create AKI.

Nevertheless, renal dysfunction per se is associated with a broad spectrum of specific metabolic alterations starting at a GFR of about 50 mL/min or lower. The main metabolic alterations are summarized in Table 35.3. Basically, AKI is a systemic syndrome in which more or less all physiologic functions, endocrine and metabolic pathways, and organ functions are affected. Moreover, the various types of RRT exert a pronounced impact on metabolism and nutrient balances (see next) (Table 35.4). Taken together, AKI often presents a proinflammatory, prooxidative, and hypercatabolic state that exerts a fundamental effect on the course of disease and development of complications and is also associated with a specific, “attributable” mortality.

Energy metabolism in patients with acute kidney injury

In experimental animals, AKI tends to decrease oxygen consumption even when hypothermia and acidosis are corrected (uremic hypometabolism) [67]. Remarkably, in the multiple organ failure syndrome, oxygen consumption is significantly lower in patients with AKI than in those without impairment of renal function [68].

In patients with uncomplicated AKI, however, resting energy expenditure (REE) is within the range of healthy subjects. In patients with sepsis and associated AKI, oxygen consumption is increased by approximately 20%−30% as compared to subjects with uncomplicated AKI [69]. Energy expenditure is remarkably similar in AKI patients without or with RRT [70].

TABLE 35.3 Important metabolic abnormalities induced by acute kidney injury.

- Increase in protein catabolism
- Peripheral glucose intolerance/increased gluconeogenesis
- Inhibition of lipolysis and retarded clearance of plasma fat
- Depletion of the antioxidant system
- Induction of an inflammatory state
- Impaired immunocompetence
- Complex endocrine abnormalities: hyperparathyroidism, insulin resistance, erythropoietin resistance, resistance to growth factors, etc.

TABLE 35.4 Enhanced protein catabolism in acute kidney failure: contributing factors.

- Impairment of metabolic functions by uremic toxins
- Acute-phase reaction—systemic inflammatory response syndrome (activation of cytokine network)
- Augmentation of inflammation by AKI
- Endocrine factors
  - Insulin resistance
  - Increased secretion of catabolic hormones (catecholamines, glucagon, glucocorticoids)
  - Hyperparathyroidism
  - Suppressed release/resistance to growth factors
- Acidemia
- Inadequate supply of nutritional substrates
- Renal replacement therapy
  - Release of proteases
  - Loss of nutritional substrates
  - Inflammatory reaction (blood−membrane interactions)

AKI, Acute kidney injury.

These data indicate that there is little if any change in energy metabolism in patients from the AKI per se, and oxygen consumption is mainly determined by the underlying disease and associated complications [71]. In contrast to several other acute disease processes, there is actually a tendency to decrease than to increase energy expenditure with AKI.

Currently available formulas for estimating energy expenditure are inaccurate in patients with AKI [70]. Measurement of REE by using indirect calorimetry is recommended by several nutrition societies which, however, at the present time, is rarely available in clinical practice [72].

Energy requirements in patients with acute kidney injury

During nutritional support of acutely ill patients, the intake of energy substrates should never exceed actual energy expenditure. Complications, if any, from slightly underfeeding are less deleterious than from overfeeding [73,74]. Increasing energy intake from 30 to 40 kcal/kg BW/d in patients with AKI increases the rate of metabolic complications, such as hyperglycemia and hypertriglyceridemia, and has no beneficial effects [75].

Patients with AKI should receive 20 to a maximum of 30 kcal/kg BW/d [76]. Even in hypermetabolic conditions such as sepsis or the MODS, energy expenditure rarely is higher than 130% of calculated basic energy expenditure, and thus energy intake should not exceed 30 kcal/kg BW/d.

During continuous RRT (CRRT) the use of citrate anticoagulation can be associated with an additional energy intake from the citrate infusion, which although difficult to quantify is estimated as up to 400 kcal/d (vide infra) [77]. These calories and other nontraditional nutritional sources of energy, such as additional glucose infusions or sedation with propofol, which contains a lipid emulsion, must be considered when calculating the energy intake in nutritional support.

Protein- and amino acid metabolism in acute kidney injury

A leading feature of the metabolic alterations of AKI is the enhancement of protein catabolism with excessive release of amino acids from skeletal muscle and sustained negative nitrogen balance [78]. Amino acids are redistributed from muscle tissue to the liver where hepatic extraction of amino acids from the circulation, hepatic gluconeogenesis and ureagenesis are increased. Moreover, protein synthesis is impaired in AKI [79].

Amino acid transport into skeletal muscle is reduced in AKI. This abnormality can be linked both to insulin resistance and to a generalized defect in ion transport in uremia [80]. Moreover, there are specific alterations of amino acid metabolism, such as the impairment of conversion of phenylalanine to tyrosine and, because circulating arginine is derived mainly from the kidney, reduced arginine synthesis [81]. The elimination of amino acids from the intravascular space is altered [82]. As expected from the increased hepatic extraction of amino acids, overall amino acid clearance and clearance of most glucogenic amino acids are enhanced, but the plasma clearance of phenylalanine, proline, and valine is decreased in AKI. As a consequence of these metabolic alterations, imbalances in amino acid pools in plasma and in the intracellular compartments occur, and a typical plasma amino acid pattern is observed in AKI [83].

Mechanisms of protein catabolism in acute kidney injury

The causes of hypercatabolism in AKI are complex and manifold and present a combination of unspecific mechanisms induced by the acute disease processes, the acute-phase reaction, the systemic inflammatory syndrome, acidemia, the underlying illness/associated complications, specific effects induced by the acute loss of renal function, and, finally, by the type and intensity of RRT (Table 35.4).

A dominant mechanism for amino acid hypercatabolism is the stimulation of hepatic gluconeogenesis [78]. In healthy subjects and in patients with advanced CKD, hepatic gluconeogenesis ceases with a sufficient infusion of exogenous glucose. In contrast, in dogs with AKI, hepatic glucose formation is only decreased but not halted by exogenous glucose, and gluconeogenesis from amino acids an associated muscle catabolism persists even during glucose infusion [84]. These findings have important implications for nutritional support in patients with AKI-3 because it is impossible to achieve a positive nitrogen balance during the acute phase of the disease.

Several additional catabolic factors are operative in AKI. The secretion of catabolic hormones (catecholamines, glucagon, glucocorticoids), hyperparathyroidism (which is also frequently present in AKI), suppression and/or decreased sensitivity to growth factors, and the release of proteases from activated leukocytes all can contribute protein breakdown [85]. An important stimulus of muscle protein catabolism is insulin resistance. In an animal model corresponding to clinical AKI-3 muscle, the maximal rate of insulin-stimulated protein synthesis is depressed and protein degradation is increased [86]. An inefficient intracellular energy metabolism also stimulates protein breakdown and interrupts the normal control of muscle protein turnover.

As in other acute disease processes, inflammatory mediators, such as tumor necrosis factor-α and interleukins, play a central role in protein and amino acid hypercatabolism. However, in comparison to other acute disease states, this inflammatory reaction is augmented in AKI, both because the kidneys play an important role in the catabolism of cytokines and because cytokine release is stimulated during tubular injury [87,88].

Metabolic acidosis is a major cause of muscle protein catabolism in CKD through activation through the glucocorticoid-dependent ubiquitin–proteasome pathway [89,90]. The role of acidosis on metabolism in the context of AKI remains to be defined and the optimal bicarbonate concentration is unknown. In patients on RRT, acid–base balance is usually well controlled and can be adjusted as desired. In addition to its negative effects on protein balance, acidosis may be associated with a broad pattern of untoward side effects, on bone and mineral metabolism, glucose tolerance, lipolysis, and hormone secretion and action.

Finally, the type, frequency, and intensity of RRT can profoundly affect protein metabolism and nutrient balances in patients with AKI. Aggravation of protein catabolism, in part, is mediated by the loss of nutritional substrates during RRT, but, both the activation of protein breakdown and the inhibition of protein synthesis in muscle can be induced by RRT (see next) [91].

Clinical studies on protein catabolism in acute kidney injury

Several studies have tried to quantify protein catabolism in critically ill patients with AKI to define the optimal intake of amino acids/protein in these patients. In most of these investigations, net protein catabolism (i.e., the difference between protein synthesis and protein degradation) was estimated by calculating urea nitrogen appearance or urea kinetics in patients on intermittent hemodialysis (HD) [92,93].

Net protein catabolism in these investigations was extremely variable and indicated that the main mechanisms of protein breakdown are much more related to the underlying disease process and associated complications and not to AKI per se. Nevertheless, as detailed previously, the presence of AKI modifies or augments the underlying inflammatory state and promotes protein breakdown.

The mean net protein catabolic rate (with abroad range of deviation) was approximately 1.5 g/kg BW/d in most investigations [94–97] but also was higher, about 2.0 g/kg BW/d in some studies [98]. Taken together, there are wide variations in net protein catabolism between individual AKI patients and also in the same patient during the course of the illness [95].

Amino acid/protein requirements in patients with acute kidney injury

The most controversial question regarding nutritional support in patients with AKI concerns the optimal intake of amino acids and protein. Only a few studies have attempted to define requirements, and there are no adequately designed and powered RCTs available in this field. A previous dogma, that protein intake should match protein catabolism, has never been confirmed in any acutely ill patient group, including in patients with AKI [99,100].

Guidelines from ASPEN in 2010 state, "intake should be adjusted according to catabolic rate, renal functions, and dialysis losses" [13]. More recent guidelines provide a "standard recommendation for protein (1.2–2.0 g/kg BW/d)" for patients without RRT and "up to a maximum of 2.5 g/kg BW/d" for AKI patients on RRT [12]. In contrast, European guidelines recommend 1.3–1.5 (with a maximum of 1.7) g protein/kg/d, which includes 0.2 g/kg/d to compensate for RRT-associated amino acid losses [14]. The level of evidence for all these recommendations is low.

The current ASPEN recommendation for a high protein intake in patients with AKI is mainly based on a study by Scheinkestel and coworkers [101]. However, this is a small and not adequately randomized trial that evaluated the effect of three levels of protein/amino acid intake (1.5, 2.0, and 2.5 g/kg BW/d) on nitrogen balance and outcome. Most patients were studied sequentially. Nitrogen balance was inversely related to energy expenditure and positively related to protein intake. Not surprisingly, nitrogen balance was positively associated with ICU- and hospital survival (but not in a multivariate analysis), and a causal relationship of the amount of protein/amino acids and clinical outcome cannot be concluded from this investigation.

Again, it must be stressed that hypercatabolism cannot be overcome by simply increasing protein or amino acid intake even in patients with normal kidney function. There are no proven benefits of excessive intakes in AKI patients, which increase the accumulation of waste products with the potential of aggravating uremic complications, inducing a hyperammonemic state, and increasing the need for dialysis that, in turn, increases nutrient losses and stimulates muscle protein degradation. Today, for nutritional research, nitrogen balance is rather a surrogate parameter than a primary endpoint.

Carbohydrate metabolism

Glucose metabolism in AKI is also affected both by nonspecific mechanisms mediated by the acute disease state and by the specific effects of acute uremia. A major abnormality is insulin resistance; plasma insulin concentrations are elevated, the maximal insulin-stimulated glucose uptake by skeletal muscle is decreased and muscular glycogen synthesis is impaired [102]. The severity of insulin resistance in patients with AKI is correlated with the mortality rate [103].

A second feature of altered glucose metabolism in AKI is accelerated hepatic gluconeogenesis mainly from conversion of amino acids released during protein hypercatabolism. Hepatic extraction of amino acids and their conversion to glucose and urea are all increased in AKI. As discussed earlier, in contrast to the nonuremic state and CKD, hepatic gluconeogenesis in AKI cannot be suppressed completely by exogenous glucose infusions [84]. Metabolic acidosis also affects glucose metabolism in AKI by further decreasing glucose tolerance.

Alterations in glucose and protein metabolism in AKI are interrelated. Several factors activating protein catabolism contribute to impairment of glucose metabolism. As a consequence of these metabolic alterations, hyperglycemia is often present in AKI, and insulin infusions for glucose management may become necessary in many patients.

Finally, the metabolism of insulin is abnormal in AKI; endogenous insulin secretion is reduced in the basal state and during glucose infusion [104]. Because the kidney is a main organ of insulin disposal, insulin degradation is decreased; but surprisingly, insulin catabolism by the liver is also consistently reduced in AKI. The resulting elevations in plasma insulin concentration may explain the normal blood glucose levels in many patients with AKI.

Lipid metabolism

AKI is associated also with specific alterations in lipid metabolism. Total plasma triglyceride concentrations and triglyceride content of plasma lipoproteins, especially VLDL, are increased, while total cholesterol and in particular HDL cholesterol are decreased [105].

The major cause of lipid abnormalities in AKI is an impairment of lipolysis. The activities of both lipolytic systems, peripheral lipoprotein lipase and hepatic triglyceride lipase, are decreased to less than 50% of normal [106]. This impairment of lipolysis in AKI is in contrast to most other acute disease states in which lipolysis usually is augmented. Nevertheless, fatty acid oxidation is not impaired in AKI [70]. Metabolic acidosis may contribute to the impairment of lipolysis in AKI by further inhibiting lipoprotein lipase.

Particles of artificial fat emulsions used in PN are degraded similarly to endogenous VLDL. Thus the nutritional consequence of the impaired lipolysis is a delayed elimination of intravenously infused lipid emulsions [107]. The clearance of fat emulsions is reduced by more than 50% in patients with AKI. Moreover, relevant for enteral nutrition is that intestinal fat absorption is retarded, at least in experimental uremia [108].

Abnormal carnitine levels or metabolism does not contribute to the development of lipid abnormalities in AKI [109]. In contrast to CKD, plasma carnitine levels often are increased in AKI. This might be mediated not only by an increased release from muscle tissues during catabolism but also by an activated hepatic carnitine synthesis. There is a substantial loss of carnitine during various RRT modalities and a deficiency both of total and free carnitine may develop during prolonged CRRT [110].

Micronutrients and the antioxidant system in acute kidney injury

Only observational studies of plasma micronutrient concentrations in various heterogeneous groups of patients with AKI are available [98,111,112]. Most of these studies were conducted in patients receiving RRT. Some studies measured micronutrient losses during RRT but in poorly defined clinical situations (vide infra) [113–115]. The results of these studies are extremely variable and in part even contradictory. In fact, little is known about the effect of AKI per se on micronutrient metabolism. Micronutrient requirements in patients with AKI are not defined, and evidence-based recommendations cannot be given.

By definition, micronutrients (water- and lipid-soluble vitamins, trace elements) are essential components of nutrition, and any nutritional regimen for patients with AKI must be complete and contain these substances. Low plasma levels do not necessarily reflect a deficiency state, because micronutrients, such as selenium or vitamin C, may be redistributed within tissues during an acute-phase reaction.

Currently available enteral nutrition preparations and solutions of vitamins and trace elements for PN solutions usually contain micronutrients in amounts recommended for healthy adults (RDA, recommended daily allowances). These quantities, however, do not necessarily meet the altered nutritional requirements that may be sometimes increased or potentially reduced for acutely ill patients with AKI. Thus extra supplementations may become necessary for several vitamins and trace elements in addition to the amounts that are provided by enteral or PN (see next). One should differentiate “replacement,” that is, providing the daily requirement of a nutrient, which may be altered in a disease state, from “supplementation,” where higher, even pharmacologic, amounts of nutrients are provided to induce defined effects (referred to as “pharmaconutrition”). Pharmaconutrition may include provision of combinations of various antioxidants [116].

Several micronutrients are components of the antioxidative defense system of the body. In patients with AKI, an increase in oxidative stress and severe depression of the antioxidative system have been reported that can be more pronounced than in other acute disease states [117]. Reactive oxygen species (ROS) are involved in tissue (and kidney) injury in various clinical contexts, and adequate replacement or even supplementation of micronutrients should deserve much closer attention that has previously been displayed [40].

Water-soluble vitamins

Plasma concentrations of several water-soluble vitamins are decreased in patients with AKI [111]. This is also observed in many other critically ill patients without AKI. A contributing factor in patients on RRT is the loss associated with extracorporeal therapy, as was shown for thiamine, vitamin C, folic acid, and pyridoxine [118–121]. Due to increased losses from RRT and the potentially increased metabolic requirements in acute disease states, it is recommended that higher amounts of water-soluble vitamins provided to acutely ill patients with AKI-2–3 [14,76].

An example is thiamine, where more than the recommended daily intake for healthy subjects may be removed by RRT [118]. Severe deficiency states of thiamine associated with symptoms such as lactic acidosis, cardiac failure, and variable neuropsychiatric symptoms have been observed in patients with AKI and CKDs [122]. The recommended amount of 3 mg/d of thiamine for healthy subjects is absolutely inadequate to both replete the deficiency state and to cover ongoing increased requirements in patients with AKI-3.

Vitamin C levels are also decreased in patients with severely ill AKI-2–3 [111]. Losses of vitamin C up to 830-mg vitamin C in a patient receiving 2 g of vitamin C have been reported [123]. The requirements for this vitamin are also higher in patients with AKI than the recommended intake for healthy adults of 50 mg/d. Care should be observed with supplementation since vitamin C is a precursor of oxalic acid and excess intake can cause secondary oxalosis. Many cases of vitamin C–induced AKI have been reported [124]. On the other hand, in some recent studies using much higher doses of vitamin C in critically ill patients, adverse renal events have not been observed [125]. Thus the optimal intake of vitamin C is subject to much controversy and remains to be defined [123].

Lipid-soluble vitamins

In patients with AKI-2–3, plasma vitamin K is normal, and plasma levels of the other lipid-soluble vitamins A, E, and D are reduced [126]. There are no RRT-associated losses for these vitamins. Vitamin E is an essential component of the antioxidative defense system. In various experimental models, vitamin E can prevent the development of renal injury. In combination with vitamin C, vitamin E supplementation reduced the risk of developing organ dysfunction in critically ill patients who did not necessarily have AKI [127].

AKI is associated with a profound vitamin D deficiency. There is impaired conversion of 25-hydroxyvitamin D to 1,25-dihydroxyvitamin D (calcitriol), and hyperparathyroidism [126,128]. Plasma concentrations of 25- and 1,25-hydroxyvitamin D and calcium are decreased, and parathyroid hormone and FGF-23 are increased [129]. Moreover, vitamin D deficiency increases the risk of AKI [130]. On the other hand, overcorrection of vitamin D deficiency may cause AKI [131]. Vitamin D deficiency and hyperparathyroidism are present in many critically ill patients [132]. However, plasma concentration of 1,25-hydroxyvitamin D is directly correlated with renal function in these patients [133].

Beyond its effect on mineral metabolism, the steroid hormone vitamin D exerts several pleiotropic effects, for example, on immune function, intestinal mucosal integrity, myocardial performance, and glucose metabolism. The optimal dose of vitamin D for patients with AKI and which forms of vitamin D are preferable for supplementation—native vitamin D_3, 25-hydroxycholecalciferol, calcitriol, or other vitamin D analogs—remain unknown. An ongoing study should shed more insight into the distorted vitamin D/mineral metabolism in patients with AKI and help to define the optimal vitamin D intake [134].

Some precaution should be taken with vitamin A supplementation in AKI patients and especially in infants. In experimental AKI, release of retinol and retinol-binding protein from the liver is increased [135]. In a study of 19 pediatric patients developing AKI after hematopoietic stem cell transplantation who required RRT, 17 displayed elevated vitamin A plasma levels during standard supplementation and showed potential (albeit poorly defined) symptoms of hypervitaminosis A [136].

Trace elements

A broad range of alterations in plasma trace element concentrations have been described in critically ill patients with AKI-2–3 with some trace elements decreased (selenium, zinc) and some increased (copper, cobalt, molybdenum) [111,113]. However, it is difficult to differentiate whether disorders in trace element metabolism are caused by renal dysfunction, by the acute disease state, and/or by inflammation.

Decreased plasma concentrations of several trace elements (e.g., selenium, zinc, or iron) in patients with AKI may be, in part, an expression of the acute-phase reaction and may not necessarily reflect a deficiency state but rather altered compartmental (tissue) distribution.

Because of the high protein binding of trace elements, their losses during RRT are usually low but may increase when albumin loss is increased, such as by using dialyzer membranes with higher molecular weight pore size cutoffs and or a high transmembrane pressure [137,138].

Plasma selenium levels may be severely depressed in patients with AKI [113]. Losses are low during intermittent HD, but during CRRT, selenium elimination can be greater than the RDA. In patients undergoing maintenance HD therapy, selenium supplementation of 300 μg after each HD session improved the antioxidative defense system [138]. Several intervention studies have been performed administering selenium to critically ill patients. The selenium dose in many studies was clearly pharmacologic (up to 2000 μg/d) that cannot necessarily be regarded as safe in renal failure patients. In a large RCT, in critically ill patients, sodium selenite (1000-μg bolus and 1000 μg/d) reduced the number of RRT-free days but had no effect on mortality [139]. High-dose intravenous selenium is no longer recommended in critically ill patients [11].

Zinc is also considered to be an important nutrient in critically ill patients, many of whom have decreased plasma concentrations. Zinc is involved in immune function, the acute-phase reaction, antioxidative defense mechanisms, glucose homeostasis, and wound healing and may have renal protective potential [41]. No clinically significant losses of zinc occur during RRT [118].

Due to its active oxidant effects, iron can promote tissue injury and contribute to the development of AKI [140,141]. In animal experiments, interventions to limit iron availability (e.g., by providing hepcidin) can prevent AKI [142]. However, in a large RCT of intravenous iron treatment for the anemia of the critically ill, the incidence of AKI was not increased [143].

Caution should be observed when infusing AKI patients with high-dose supplements of trace elements. Parenteral infusion of trace elements into AKI patients circumvents both regulatory elements of trace element homeostasis: intestinal absorption and renal excretion so the risk of inducing an overdose with toxicity may be higher than in other patient groups. Standard infusion solutions and dialysate itself may be contaminated with several trance elements, such as manganese, zinc, copper, or chromium [112,118]. In the absence of specific studies of micronutrient requirements in AKI, a standard intake of RDA is recommended for patients with AKI as it is for other critically ill patients [14].

Other electrolytes

Derangements in electrolyte balance in patients with AKI can be affected by a broad spectrum of factors. In addition to the type and degree of kidney dysfunction, these factors include the residual GFR, the underlying diseases, severity of hypercatabolism, type and intensity of RRT, medicinal drug therapy, and also the timing, type, and composition of nutritional support.

Electrolyte requirements not only vary considerably between patients but also can fundamentally change during the course of the disease. In nonoliguric patients, subjects on CRRT and patients who are in the polyuric phase of AKI, electrolyte requirements can be considerably increased. Thus even more than other substrates, electrolyte requirements should be evaluated in each individual AKI patient on a day-to-day basis, and intakes may need to be adjusted frequently.

It should be noted that many electrolyte derangements, and especially hypokalemia, hypophosphatemia, and hypomagnesemia, increase the risk of developing organ dysfunction, including AKI. Thus avoidance of electrolyte derangements (for instance, as a results of refeeding syndrome) must constitute a primary focus of the metabolic care of patients with or at risk for AKI (vide supra).

Potassium: AKI often is complicated by hyperkalemia because of impaired urinary excretion, increased potassium release during protein hypercatabolism, and altered distribution between intra- and extracellular spaces caused by the uremic state per se, by acidosis, and by drugs such as digitalis glycosides or beta-antagonists. Therapy of metabolic acidosis may decrease the requirement of RRT by reducing plasma potassium concentrations [29]. However, many patients with AKI may present with decreased serum potassium. When correcting hypokalemia in an

AKI patient, potassium repletion must be performed at a lower rate than in nonrenal patients to avoid inducing overshoot hyperkalemia.

Phosphorus: In contrast to CKD, hyperphosphatemia usually is of minor relevance in patients with AKI. Nevertheless, hyperphosphatemia per se can cause AKI by precipitation of calcium phosphate crystals within the kidneys (acute phosphate nephropathy). This can be due either to release of phosphate from cells (such as in tumor lysis syndrome) or by excess intake of phosphate (e.g., by phosphate-rich enemas) [144].

In patients receiving RRT, hypophosphatemia is much more relevant and common than hyperphosphatemia. Inadequate intake, internal redistribution due to inflammation, and increased losses, mainly through RRT (especially with phosphate-free RRT), can contribute to decreased plasma phosphate concentrations. Hypophosphatemia is associated with many side effects, including respiratory failure, difficulty weaning from mechanical ventilation, decreased cardiac contractility, and increased risk of infections, attention should be paid to providing adequate phosphate supplementation and the use of phosphate-containing replacement fluids [145,146].

Hypophosphatemia can be a consequence of the refeeding syndrome [55]. Since patients with AKI may be given nutritional support that is phosphate free, plasma phosphate can fall precipitously particularly when such nutritional therapy is given to subjects with severe malnutrition.

Calcium: The majority of patients with AKI-2−3 are hypocalcemic with a reduction of both protein-bound and ionized fractions [147]. In most critically ill patients, the degree of hypocalcemia correlates with the severity of illness. The causes of hypocalcemia are manifold and can include hypoalbuminemia, hyperphosphatemia, citrate anticoagulation, the impaired formation of 1−25 $(OH)_2$ vitamin D_3 with reduced intestinal calcium absorption, and, potentially, skeletal resistance to parathyroid hormone. During citrate anticoagulation hypocalcemia may develop due to the chelation of calcium by citrate; parathyroid hormone secretion may increase if calcium is not adequately replaced [148].

Hypercalcemia may be caused by high dialysate calcium concentrations, immobilization, acidosis, and/or hyperparathyroidism. In AKI caused by rhabdomyolysis, persistent elevations of serum calcitriol may result in a rebound hypercalcemia during the diuretic phase. Acute hypercalcemia per se can cause AKI by inducing acute nephrocalcinosis, arterial calcifications, and interstitial nephritis.

Magnesium: Hypomagnesemia occurs frequently in patients with AKI and may be caused by the acute illness per se, the use of magnesium-free replacement fluids for hemofiltration, and citrate anticoagulation, and increased urinary magnesium losses that may occur during the diuretic phase of AKI and after renal transplantation. Several nephrotoxic drugs, such as cisplatin, aminoglycosides, and amphotericin B, may cause renal magnesium wasting [149].

Magnesium deficiency may aggravate renal tissue injury. In contrast, magnesium repletion may be protective, especially after exposure to nephrotoxins [150]. Sometimes potassium depletion may occur with hypomagnesemia. In these circumstances the hypokalemia can only be corrected when magnesium and potassium are replenished [151].

Clinically important elevations of serum magnesium are rare in patients with AKI. Symptomatic hypermagnesemia can develop with high magnesium intakes given with oral, enteral, or PN.

Effect of renal replacement therapy on body metabolism and nutrient balances

The effect of various modalities of RRTs on body metabolism and nutrient balances are manifold and are mediated by treatment-associated nutrient losses, bioincompatibility of dialyzer membranes and tubing, activation of various signaling cascade systems, and the release of cytokines, which ultimately induce an inflammatory reaction [113] (Table 35.5).

Intermittent hemodialysis

Most patients with community- and hospital-acquired AKI are treated with conventional intermittent HD. During HD, several water-soluble molecules, such as amino acids, water-soluble vitamins, and carnitine, are lost (vide supra) [120]. Amino acid loss accounts for approximately 2 g/h dialysis session.

Protein catabolism is stimulated not only because of these amino acid losses but also by activation of protein breakdown. Various inflammatory markers rise during HD and this rise—along with the stimulation of protein catabolism—persists until several hours after end of HD [152,153]. Moreover, HD induces an oxidative stress and generation of ROS that is augmented by the associated losses of nutritional antioxidants [154].

In sharp contrast to CKD patients, patients with AKI are at risk of developing hypophosphatemia during HD, and this is associated with impaired prognosis [155].

Continuous renal replacement therapy

In many critical care units, CRRT is the preferred modality of RRT for treatment of patients with AKI.

TABLE 35.5 Metabolic effects of renal replacement therapy in acute kidney injury.

Intermittent HD

- Loss of water-soluble molecules
  - Amino acids
  - Water-soluble vitamins
  - L-Carnitine etc.
- Activation of protein catabolism
  - Loss of amino acids
  - Loss of proteins and blood
  - Induction of inflammation/cytokine release (TNF-α etc.)
- Inhibition of protein synthesis
- Increase in ROS-production

CRRT

- Heat loss
- Excessive load of substrates (lactate, citrate, glucose, etc.)
- Loss of nutrients (amino acids, vitamins, selenium, etc.)
- Loss of electrolytes (phosphate, magnesium)
- Elimination of peptides and proteins (hormones, mediators, albumin)
- Consequences of bioincompatiblity (induction/activation of mediator-cascades, of an inflammatory reaction, stimulation of protein catabolism)

CRRT, Continuous renal replacement therapy; *HD*, hemodialysis; *ROS*, reactive oxygen species; *TNF-α*, tumor necrosis factor-α.

Because of the continuous mode of therapy and associated high fluid turnover of up to 60 L/day or more, this treatment modality may induce a broad pattern of metabolic consequences (Table 35.5).

A relevant side effect of CRRT is the elimination of small- and medium-sized molecules. These losses are extremely variable depending on the mode, membranes used, dose, duration of the therapy, and the type of anticoagulation, so approximate values can only be given.

In the case of most amino acids, the sieving coefficient approaches 1.0, so the loss of amino acids can be estimated from the volume of the filtrate and the average plasma concentrations. However, because of the electric charges of several amino acids and the characteristics of the filtration membrane, the sieving coefficient can also exceed 1.0, such as for glutamine and arginine, which are the amino acids with the highest losses during CRRT [156].

Usually, amino acid losses amount to approximately 0.2 g/L filtrate. Depending on the filtered volume, this can account for a total loss of 5–15 g amino acids per day, representing about 10%–15% of the amino acid intake. Amino acid losses during continuous hemofiltration (CVVH) and continuous HD (CVVHD) are of a similar magnitude [156,157]. In a more recent study, amino acid losses of 5.13 g were measured during one HD session, losses of 8.21 g during 12 hours of slow efficiency dialysis, and 18.7 g during 24 hours of CRRT [113].

What often is ignored is the fact that, depending on the type of therapy, the dialyzer membrane material and the effective transmembrane pressure can contribute to additional protein losses of up to 20 g/day.

Water-soluble vitamins, such as thiamine, folic acid, vitamin B6, and vitamin C, are also eliminated during CRRT, and an intake above the RDA is required to maintain plasma concentrations of these vitamins in patients with AKI (see previously).

Because of the high protein binding, losses of trace elements during RRT usually are low but can become clinically important with modern high-flux membranes, if high transmembrane pressures are used, or if there is a leak of albumin and other proteins. Selenium losses by convective transport during CRRT can be higher than the RDA [118] (see previously).

Glucose balance during CRRT is dependent on the glucose concentration of the replacement fluid. Solutions designed for peritoneal dialysis should not be used for CRRT, because they promote excessive glucose uptake. Dialysate glucose concentrations should range between 1 g and 2 g/dL to maintain a zero glucose balance.

Uptake of lactate, the organic anion present in some replacement fluids during CRRT, can be considerable and within the range of endogenous lactate turnover. During disease states associated with increased lactate formation (such as cardiogenic shock) or decreased lactate clearance (liver insufficiency), bicarbonate-based replacement fluids should be used to prevent excessive rises in plasma lactate concentrations.

Recently, in several countries, citrate anticoagulation has become standard for RRT of AKI patients. Since citrate is predominantly catabolized in the liver, liver dysfunction can result in decreased citrate clearance, and citrate utilization must be monitored, for example, by monitoring the total: ionized serum calcium ratio. Citrate also serves as energy source and an additional energy intake of up to 400 kcal/d is associated with the use of citrate anticoagulation [77].

Special attention should be paid to electrolyte balances during CRRT. Depending on the filtration rate and duration of CRRT, the risk of inducing hypokalemia and especially hypophosphatemia can be very high (see previously). Even at low-intensity CRRT (e.g., a filtration rate of 25 mL/kg/h), 54% of patients developed hypophosphatemia and 24.5% developed hypokalemia [158].

Patients with AKI treated by RRT should be given also be given intravenous nutrition at least during the extracorporeal therapy. The endogenous clearance of amino acids is in the range of 80−1800 mL/min and thus exceeds dialytic clearance by 10−100 times. Nutritional infusion during RRT results in minimal increases in plasma amino acid concentrations, and therefore only a small fraction, about 10% of the amino acids infused, will be removed by the RRT, in addition to the basal amino acid losses that would occur without the amino acid infusion.

The role of nutritional status and nutrient supply on clinical outcome

As in other acute and chronic diseases in patients with AKI, a poor nutritional state is associated with an increased risk of complications and an impaired prognosis [159]. In a large study, preexisting severe malnutrition is present in 42% of patients with AKI and is associated with such complications as sepsis and septic shock, hemorrhage, cardiac arrhythmias, cardiogenic shock and respiratory failure, prolonged hospital stay, and increased hospital mortality [160]. Both sarcopenia and decreased muscle strength are each associated with a poor outcome [161].

Obesity, on the other hand, increases the risk of developing AKI [162]. However, a high body mass index confers a protective role and improves prognosis in patients with AKI (obesity paradox) [162,163]. Since obesity is often associated with deficiency states of various nutrients and with protein wasting (such as “sarcopenic obesity”), nutrition support should not be withheld in overweight or obese patients with AKI.

Practical issues concerning clinical nutrition in patients with AKI-3 requiring RRT

General considerations

The practice of nutritional support in AKI patients is not fundamentally different from that in patients without renal dysfunction. However, as detailed previously, the nutritional regimen should be adapted to the altered metabolism and nutrient requirements and nutrition must be coordinated with RRT.

The optimal intake of nutrients in patients with AKI is influenced more by the nature of the illness causing AKI, the extent of catabolism, and the type and frequency of RRT rather than renal dysfunction per se. In most clinical situations, daily requirements will exceed the minimal intake recommended for stable nondialyzed CKD patients or the RDA for normal subjects.

Nutrient requirements are summarized in Table 35.6. It must be stressed that these are approximate values

TABLE 35.6 Nutrient requirements in acute kidney injury-3 requiring renal replacement therapy (RRT)[a].

Energy intake	20− 25 (max. 30)	kcal/kg/d
Glucose	3−4	g/kg/d
Lipids	0.8−1.2	g/kg/d
Amino acids/protein		
+ RRT	1.2−1.5	g/kg/d
+ Hypercatabolism	(Max. 1.7)	g/kg/d
Vitamins	(Combination products proving RDA)	
Water soluble		2 × RDA/d
Lipid soluble		1−2 × RDA/d (higher for vitamin D?)
Trace elements	(Combination products proving RDA)	
		1 × RDA/d
Electrolytes	(Requirements must be assessed individually)	
	(Beware of: hypokalemia and hypophosphatemia)	

[a] *Requirements differ between individual patients and may vary considerably in the same patient during the course of the disease.*
RDA, Recommended dietary allowances.

only which are not based on high-quality RCTs but on expert opinion (i.e., "weak evidence, low level of recommendation"). Patients with AKI present an extremely heterogeneous group of subjects with widely differing nutrient requirements, and these needs may differ considerably between individual patients and may vary greatly during the course of disease in the same patient. So individual daily assessments of nutrient requirements are mandatory.

Oral nutrition in patients with acute kidney injury

Oral nutrition should be encouraged whenever possible, and this is often feasible in noncritically ill, noncatabolic patients presenting with AKI as mono-organ dysfunction who are mostly cared for on open wards.

The dietary goals in these stable patients are similar to those for CKD patients (see the chapter on nutrition in HD). In patients not requiring RRT the diet should start with about 0.4 g (high-quality) protein/kg BW/d and be gradually increased to about 1.0 g/kg BW/d as long as the SUN remains below 80 mg/dL. In patients requiring RRT, protein intake should be increased to 1.2–1.4 g/kg BW/d. Patients should receive an adequate intake of water-soluble vitamins and vitamin D, and electrolyte balance must be maintained.

In patients who do not eat adequately the provision of liquid diets or ONS may be used to improve total nutrient intake. Commercially available diets designed for patients with CKD can be used for this purpose (see next). For patients with CKD-3–5, protein and electrolyte restricted diets are available. These diets with a moderately increased amount of protein but with lower electrolyte content (i.e., potassium, magnesium, and phosphate restriction) can be used for patients requiring RRT. Some of these diets have other nutrients added, such as carnitine, and are enriched with various flavors to improve the taste.

During the dialysis session, patients can be encouraged to eat or to drink liquid diets or supplements (intradialytic enteral nutrition) (see next).

Enteral nutrition

Enteral nutrition is also the preferred route of nutritional support for AKI patients who are unable to eat foods. The advantages of enteral nutrition are manifold and include the support of intestinal defense functions against translocation of bacteria, the support of the enteric immune system, and, thus ultimately, the reduction in infectious complications.

Enteral nutrition may confer an additional advantage with regard to recovery of renal function. In experimental AKI, enteral nutrition as compared to PN has been shown to accelerate recovery of renal function [164]. In clinical studies on outcome in AKI patients requiring RRT, enteral nutrition was associated with an improved survival [165].

In AKI patients the effect of acute kidney dysfunction on the gastrointestinal function, and especially on gastrointestinal motility, is of crucial importance with regard to the ability to provide enteral nutrition. A broad spectrum of gastrointestinal abnormalities have been described in uremia, but unfortunately, few studies have examined these disorders in AKI. It is known that AKI gastric emptying is retarded and intestinal transit time is prolonged [166].

Acute disease states and postoperative and posttraumatic conditions are also associated with impaired motility in various segments of the gastrointestinal tract. In the critical care setting, these disorders can be augmented by an increase in intraabdominal pressure and by various medicines. Sedation therapy, analgesia using opiates, catecholamines, and other medicines may contribute to impaired intestinal motility [167].

Thus, in many patients with AKI, the acute kidney dysfunction in combination with these various other factors can profoundly impair gastrointestinal motility and compromise one's ability to attain dietary goals with enteral nutrition. Many patients with AKI will require drugs that enhance motility, both at the level of the stomach and the small and large intestines. Again, this aspect of gastrointestinal function has not been specifically investigated in patients with different stages of AKI. In critically ill patients, erythromycin at a low dose (1–2 mg/kg BW up to thrice daily) may effectively stimulate motility both at the gastric and the intestinal levels. An alternative approach is to use a combination of metoclopramide (for promotion of gastric emptying) and parasympathomimetics such as neostigmine (for stimulation of intestinal motility). Several others drugs currently are under investigation [11,167]. Prokinetic drugs should be given early, if not prophylactically, to facilitate the early use of enteral nutrition.

If it is not possible to adequately stimulate motility with these medicines, the placement of a postpyloric jejunal tube should be considered. With this approach, it is often possible to achieve the nutritional goals. However, there still remain a considerable number of patients who cannot be fed per the enteral route alone and who will require supplemental or even total PN (see next).

Enteral diets for the patient with acute kidney injury

There are no commercial diets that have been specifically developed for AKI patients. Three types of diets have been used for this patient group:

1. Elemental amino acid diets (mostly powder): These diets were originally designed for supplementation of low-protein diets with essential amino acids for stable CKD patients. They should not be used for AKI patients because these diets are incomplete and inadequate for acutely ill patients who have increased nutrient requirements.
2. Standard liquid diets that are used for nonuremic patients.
3. Liquid formula diets that (1) have a reduced protein and electrolyte content and are adapted to the needs of CKD-3–5 patients who do not require RRT or (2) that have a moderately increased in protein content, are reduced in electrolytes (potassium, phosphate, magnesium, sodium) designed for patients on RRT and that may contain other nutrients, such as carnitine.

In general, the standard diets recommended for other critically ill patients are also recommended for critically ill patients with AKI [13,14]. It should be noted that in acutely ill patients on RRT, hyperkalemia or hyperphosphatemia are rarely clinically relevant problems; so the use of electrolyte restricted diets usually is not mandatory. These diets contain the RDA of micronutrients only for healthy subjects, and care should be taken that water-soluble vitamins, vitamin D and possibly also selenium and zinc, are supplemented adequately.

Immunonutrition: Whether the addition to enteral nutrition preparations of such potential immunomodulating substrates, as fish oil, antioxidants, nucleotides, or glutamine, has advantages for patients with AKI remains unknown. The main indications for the use of these immunomodulating supplements diets are perioperative situations, but they are not recommended for critically ill patients with a high severity of illness (i.e., APACHE II Score >25) [11,12].

Enteral diets should contain dietary fiber (water soluble or insoluble). This is not recommended so much to reduce uremic toxicity and the inflammatory state, as has been suggested for CKD patients, but for the metabolic effects, the protective actions of short-chain fatty acids on the colon, and the promotion of intestinal motility [168].

Feeding tubes: Fine pore nasogastric feeding tubes are a standard feature of enteral feeding. Because feeding tubes are often used for extended periods of time, these tubes should be made of tissue-friendly material, such as silicone or polyurethane, and not of polyvinylchloride that can cause ulcerations in the upper digestive tract.

As discussed previously, postpyloric feeding tubes should be considered in patients with severe gastrointestinal intolerance and high gastric residual volumes. The tube tip should be positioned well after the ligament of Treitz; the end of the feeding tube should not be positioned in the duodenum. Postpyloric tubes should have a second lumen for gastric decompression and administration of medicines into the stomach. Self-advancing (in part electromagnetically visualized) tubes are available that can be positioned within an acceptable time frame (with some experience within less than 20 minutes) and without the need for endoscopy [169].

Enteral nutrition should be started early; that is, within 24 hours after admission, at a low rate of infusion and gradually increased over 5–7 days [43].

Stress ulcer prophylaxis: Enteral nutrition confers some protection against the development of stress ulcers and gastric bleeding. Patients with AKI usually are high-risk patients for gastric ulcers; hence in many AKI patients, ulcer prophylaxis, preferably with proton pump inhibitors, will be necessary.

Clinical studies of enteral nutrition in patients with acute kidney injury

In sharp contrast to the worldwide daily routine practice of enteral nutrition in patients with AKI, very few systematic studies have been performed on these patients. There is only one major study evaluating enteral nutrition in AKI. This was more of a feasibility study that compared patients without AKI (control group) to patients with AKI who were or were not receiving RRT [170]. As compared to patients without renal dysfunction, patients with AKI had higher gastric residual volumes, and there was a trend to more frequent withdrawal of enteral nutrition due to complications. A standard enteral formula was used, which was partially adapted for CKD patients. But because of lack of randomization, no conclusions can be drawn concerning the advantages of such adapted diets. In general, the enteral nutrition was well tolerated, and the rate of nutrient delivery was similar comparable among all groups.

Parenteral nutrition in acute kidney injury

Historically, most studies of nutritional support in AKI patients were performed using PN. However, because of its well-defined advantages, enteral nutrition should be preferred whenever possible. Nevertheless, for many reasons, as discussed previously, in a considerable fraction of AKI patients, it may not be feasible to provide adequate nutrition enterally and supplemental or total PN may be necessary. However, even when PN becomes mandatory, a minimal amount of enteral nutrition (trophic or trickle nutrition) should be attempted whenever possible to support intestinal function.

In general, it is recommended that PN be started not earlier than 3–7 days after admission [12]. However, in patients with AKI and malnutrition and in patients requiring RRT, especially for those undergoing intensive dialysis treatment, which is associated with larger nutrient losses, it may be inappropriate to delay PN, and it should be started earlier. The progressive increase in PN to the desired levels should be slower than has been recommended in the past. The final infusion volume and nutritional goals should not be attained until 5–7 days after initiation of PN [11].

It should be noted that the nutrients infused are not toxic. Many of the negative side effects associated with the PN are due to inadequate planning, for example, excessive energy intake, solutions lacking one or more key nutrients, too rapid an increase in the infusion rate, too high an infusion rate, or insufficient monitoring (e.g., leading to hyperglycemia) rather than to the parenteral route of nutrient supply per se. Properly performed PN is not associated with a higher rate of complications than enteral nutrition [171].

Components of the parenteral nutrition solution

Amino acid solutions: In the early days of nutritional support of AKI patients, amino acid solutions containing only essential amino acids were used. This practice was based on the concept of diets providing very low amounts of protein diet or essential amino acids for the treatment of CKD patients. These amino acid solutions are incomplete, have an unbalanced composition, and in large amounts (i.e., >40 g or essential amino acids per day with no nonessential amino acids) may cause such life-threatening complications as hyperammonemic coma. They have been abandoned in favor of solutions containing essential and nonessential amino acids.

The standard complete amino acid solutions that are used for patients without renal dysfunction are recommended for patients with AKI. In several countries, specific amino acid solutions adapted to the metabolic alterations of AKI are also available [66]. These solutions may contain different combinations of essential and nonessential amino acids and higher concentrations of conditionally essential amino acids. Some of these solutions are supplemented with a tyrosine containing dipeptide, such as glycyl-tyrosine, as a source of this conditionally essential amino acid in uremia. The advantage of the dipeptide is its greater solubility; tyrosine has a low solubility in water and cannot be added to an amino acid solution as the free amino acid in adequate amounts [81]. Beyond normalizing the plasma amino acid pattern and improving nitrogen balance, whether these modified solutions can improve clinical outcome remains to be shown. In general, disease-specific amino acid solutions are not recommended for the nutritional support of critically ill patients [11,12].

In animal experiments, it has been demonstrated that amino acids imbalances exert negative effects not only on protein metabolism but also on more complex cellular functions such as signaling pathways and gene activation [172]. These new insights may potentially stimulate a renewed interest in disease-modified amino acid solutions.

For the hypercatabolic critically ill patient glutamine has been regarded as a conditionally essential amino acid. An intake 0.3 g glutamine/kg BW/d has been recommended for these patients. Since free glutamine is not stable in aqueous solutions, glutamine-containing dipeptides (such as alanyl-glutamine) are used as the glutamine source in PN. Several recent studies, however, have not demonstrated beneficial effects of glutamine supplementation [173]. In a secondary analysis of a large RCT, patients with renal injury who were randomized to receive glutamine had a higher mortality [65]. In recent recommendations, renal failure, as with hepatic failure, is considered to be a contraindications for glutamine supplementation [11,12].

Glucose: Glucose should be the main energy substrate. In contrast to earlier recommendations, glucose intake must be restricted to 2 to a maximum of 4 g/kg BW/d. This is recommended because additional glucose above these doses may not be oxidized yielding energy but may be directed to lipogenesis with fatty infiltration of the liver. Higher glucose doses may also produce excessive carbon dioxide, promoting hypercapnia in patients with reduced pulmonary function and impair immunocompetence, thereby increasing the risk of infectious complications.

Glucose tolerance is decreased in AKI, and infusion of insulin is frequently necessary to prevent hyperglycemia, which presents not only a risk factor for complications (especially infections) but also for renal injury and other organ complications (vide supra). The therapeutic target during nutritional support in the critically ill is no longer normoglycemia, however. Plasma glucose levels should not exceed 180 mg/dL [12]. It should be noted that during PN, insulin requirements are approximately 25% higher than during enteral nutrition. The amount of glucose infused and, hence, the risk of developing hyperglycemia can be reduced by limiting energy intake and providing a portion of the energy by lipid emulsions.

Lipid emulsions: The changes in lipid metabolism associated with AKI should not prevent the use of lipid emulsions, but the amount infused must be adjusted to the patient's capacity to clear and utilize lipids. Plasma triglyceride concentrations should be monitored regularly. Usually, 1 g fat/kg BW/day will not increase plasma triglycerides substantially.

Conventional lipid emulsions mostly contain plant oils (soy oil, safflower oil) with a high content of polyunsaturated omega-6 fatty acids (PUFA). PUFA-derived eicosanoids may exert proinflammatory, vasoconstrictor, and thrombocyte proaggregatory effects. There is an ongoing discussion as to whether lipid emulsions with a lower content of these PUFA (e.g., partly replacing soybean oil with olive oil, fish oil, or medium-chain triglycerides) are preferable for PN in critically ill patients [174]. Alternative oils, and especially fish oil–containing omega-3 fatty acids, can serve as precursors for potentially more beneficial eicosanoids and—importantly—for a novel class of lipid mediators, protectins, and resolvins, which are essential for the resolution of an inflammatory process [175]. In the experimental situation, fish oil can exert nephroprotective actions and prolong survival [54]. Again, systematic clinical studies in patients with AKI are not available.

Nevertheless, in several countries, such modified lipid emulsions containing a variable mixture of various oils (soy oil, coconut oil, olive oil, fish oil) have become available recently, and various international nutrition societies recommend the use of these modified lipids in PN [174].

Micronutrients: PN solutions must be complete and thus must contain all essential micronutrients. Multivitamin and multitrace element preparations are available that can be added directly to the nutrition solution. As discussed previously, double amounts of water-soluble vitamins should be provided. If higher selenium supplements are to be infused, an extra infusion should be employed for selenium, because of potential nutrient interactions (e.g., between vitamin C and selenium). Increased amounts of vitamin D or its analogs also should be provided to cover the greater requirement for this vitamin.

Electrolytes: Electrolyte requirements must be carefully assessed on a day-to-day basis and must be adapted individually. Electrolytes to handle basal requirements can be added to the nutrition solution. More pronounced electrolyte deficits may be covered with separate infusions.

PN solutions: The use of total nutritional admixtures (all-in-one solutions) has become standard worldwide. These solutions either are standard products provided by the pharmaceutical industry, usually in multichamber bags (MCBs) with a long shelf life or custom-made by the hospital pharmacy or compounding companies. The use of MCBs helps to reduce costs and also the risk of infection [176]. Usually, these MCBs contain basic solutions containing the three macronutrients, glucose, amino acids, and a lipid emulsion, and variable amounts of electrolytes. Water- and lipid-soluble vitamins, trace elements, and other electrolytes are be added as required before use.

When enteral nutrition is not possible, PN should also be started early in patients with AKI. To ensure maximal nutrient utilization and to avoid metabolic derangements, the infusion should be started at a low rate (see previously), providing about 30% of requirements initially and gradually increasing over several days. The nutrition solution should be infused continuously over 24 hours to ensure optimal substrate utilization and to avoid marked changes in substrate concentrations in patients who may have decreased ability to utilize the nutrients.

Clinical studies on parenteral nutrition in patients with acute kidney injury

As with enteral nutrition, there are a distressingly low number of systematic studies evaluating PN in patients with AKI. Several older studies assessed isolated aspects of intravenous nutrition, such as the optimal types of amino acids to be infused solution (e.g., only essential amino acids vs essential and nonessential amino acids), the severity of protein catabolism, the optimal intake of amino acids and protein, but systematic outcome studies have not been performed during the last 25 years.

It should be noted that most of these older studies do not meet current standards and practice of nutritional therapy in acutely ill patients with respect to the type and quantity of the amino acids infused, the energy intake, or the overall composition of the nutrition solution. All studies were markedly underpowered to assess hard endpoints such as survival or recovery of renal function. Moreover, in some of these studies, the control group received no nutrition at all or were given glucose alone.

Some of these prospective randomized studies are shortly summarized.

Abel et al. randomly assigned 53 patients with AKI to receive either a mean of 16 g/d of essential amino acids with hypertonic glucose or hypertonic glucose alone [177]. The survival rate was greater in patients receiving essential amino acids and this was especially seen in the sicker patients with serious complications and who required dialysis therapy.

Similarly, Feinstein et al. assigned 30 patients with AKI to three groups, to receive glucose alone, glucose and 21 g/d of essential amino acids, or glucose and 21 g/d essential plus 21 g/d nonessential amino acids [100]. In general, results were inconclusive, but there was a trend toward better nitrogen balance and clinical outcome in patients receiving more amino acids.

In a further prospective trial the same group of authors compared in an even smaller group of 13 AKI patients PN providing 21 g/d of essential amino acids with a solution with a higher amino acid intake (an amount of essential plus nonessential amino acids that was approximately equal to the urea nitrogen appearance rate) [178]. The purpose of this exploratory study was to examine the effect of these amino acid intakes on nitrogen balance in AKI patients. Nitrogen balance was not different and, as was expected in this small trial, recovery of renal function and mortality were comparable.

Some of the newer studies that have tried to assess the severity of protein catabolism and define protein and energy requirements in patients with AKI are described earlier.

In general, uncontrolled cohort studies (prospective or retrospective) support the view that an early high energy and protein intake is associated with improved survival [98,179−181]. This, however, is probably reflection of “reverse causality” since it is usually more difficult to infuse adequate amounts of nutrition into sicker patients. Prospective studies (usually subanalyses of larger trials) have all demonstrated that a slow buildup is associated with an improved outcome [44,64,182,183].

In conclusion, there are no recent systematic, randomized prospective trials of PN in AKI patients using current standards of nutritional support. Therefore no evidence-based recommendations based on randomized controlled clinical trials can be given for AKI patients. But recommendations can be made for AKI patients that are based on studies of acutely ill patients in general with some adaptations made for patients with AKI [13,14].

Intradialytic enteral or parenteral nutrition in patients with acute kidney injury

Intradialytic oral or PN (IDPN) has been shown to revert the catabolic effects of an HD treatment into an anabolic condition in clinically stable chronic HD patients [184]. Several nutritional indices can be improved by using ONS or IDPN at least in chronic HD patients [185].

For AKI patients who are cared for on an open ward without adequate oral intake, IDPN may offer a possibility to improve total nutrient intake, not so much to improve the patient’s nutritional status but rather to prevent the further loss of lean body mass during the acute disease process. However, it must be noted that, again, no studies are available in this specific acutely ill patient group that examine the effects of this treatment.

Complications of nutritional support in patients with acute kidney injury

Side effects and complications of nutritional support in patients with AKI are not fundamentally different from those in other patient groups. However, for reasons discussed previously, the risk for essentially all nutrition-associated complications is increased in the AKI patient.

Gastrointestinal side effects are more frequent, gastric residual volumes are increased, the general tolerance to enteral nutrition is decreased, and, thus, close monitoring of enteral nutrition therapy and the institution of measures to improve gastrointestinal motility and tolerance to enteral nutrition is mandatory.

Because of the compromised immune function in AKI, infectious complications originating from the central venous catheter are more frequent. RRT per se presents an additional risk factor for infection in AKI patients. Tolerance to excessive fluid volumes is impaired. Careful fluid balance must be observed, and excess infusion of fluid should be avoided. Overhydration has been recognized recently as an important factor associated with poor outcome [186]. In contrast to common thinking, overhydration also impairs renal function.

Obviously, electrolyte imbalances are frequent in AKI patients. It should be noted, however, that not only excess but also deficiencies of electrolytes, especially for phosphate and potassium, are often present in these patients. Metabolic complications frequently occur in patients with AKI because utilization of essentially all nutrients is altered or impaired. The risk for both hyperglycemia and hypertriglyceridemia is increased in AKI patients as compared to other patient groups. One reason for gradually increasing the infusion rate of the nutritional solution is to avoid many of the side effects and complications associated with nutritional support in AKI patients.

Monitoring nutritional support in patients with acute kidney injury

Because of the limited tolerance to various nutrients and the high risk of inducing metabolic derangements in AKI patients, nutritional therapy requires a tighter

TABLE 35.7 A minimal suggested schedule for monitoring plasma or serum during nutritional support.

	Patients who are metabolically	
Variables	**Unstable**	**Stable**
Glucose, potassium	1–6 × daily	Daily
Phosphate	1–3 × daily	3 × weekly
Sodium, chloride	Daily	3 × weekly
Calcium, magnesium	Daily	3 × weekly
Osmolality	Daily	1 × weekly
SUN/SUN rise/day	Daily	3 × weekly
Triglycerides	Daily	2 × weekly
Blood gas analysis/pH	1–3 × daily	1 × weekly
Urea nitrogen appearance/estimate of protein catabolism	2 × weekly	1 × weekly
Ammonium	2 × weekly	1 × weekly
Transaminases + bilirubin	2 × weekly	1 × weekly

schedule of close monitoring than in other patient groups. Table 35.7 summarizes laboratory tests that are used to monitor nutrition support to avoid metabolic complications. The frequency of testing will depend on the metabolic stability of the patient. Concentrations of plasma glucose, potassium, and phosphate should be monitored repeatedly after initiating nutritional therapy.

Glucose control: As discussed earlier, hyperglycemia presents a risk factor for kidney dysfunction in acute disease states. On the other hand, AKI per se is associated with insulin resistance. Hence, glucose control by insulin infusion is mandatory in most acutely ill AKI patients. In contrast to earlier recommendations, however, glucose control should not be too tight and should not aim for normoglycemia. Rather the goal should be to maintain plasma glucose concentrations below 180 mg/dL. Optimally, an algorithm for glucose control should be followed.

Triglycerides: Due to the impairment of lipolysis and retarded plasma clearing capacity for triglycerides, adaptations to lipid infusion can become necessary. Simultaneous infusion of propofol, which is frequently used for sedation therapy and is a drug that is dissolved in a 10% lipid emulsion, can lead to increased plasma lipid levels. This should be considered when designing the nutritional regimen.

Electrolyte balance: It is a commonplace that AKI is associated with various electrolyte imbalances, and a close monitoring schedule is mandatory. Nevertheless, it again should be stressed that the risk of deficiency states is increased in AKI for some electrolytes, particularly potassium and phosphate.

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C H A P T E R

36

Nutritional prevention and treatment of urinary tract stones*

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Epidemiology of stones

The field of kidney stone prevention is still in its infancy with a relative paucity of high-grade, evidence-based data suitable for inclusion in this chapter. Luckily, numerous studies regarding treatment and best outcomes are underway and robust, evidence-based data should become increasingly available [1]. Insights from genetics, understanding of microbiota, and an appreciation of the "exposome," the accumulation of environmental exposures during a lifetime, are contributing to our understanding of kidney stone disease as a chronic metabolic condition marked by acute episodes [1].

Kidney stones are becoming more common and are associated with significant morbidity. The overall prevalence of kidney stones has increased in the United States from 3.8% of the population in 1976–80 to 8.8% of the population in 2007–10 based on NHANES data [2]. Non-Hispanic white men have the highest prevalence of stones, followed by Hispanic men, non-Hispanic white women, and Hispanic women. Non-Hispanic Black men and women have the lowest prevalence of stones at 4.8% and 4.2%, respectively. The prevalence of kidney stones increases with age: 16% of men and 7% of women over the age of 70 had passed at least one stone in their lifetime. The prevalence of kidney stones increased in men until the age of 65, and in women until the age of 70 [3]. In a group of calcium oxalate stone formers, the prevalence of diabetes mellitus, hypertension, and increasing BMI, all risk factors for stone disease, increases from age 18 to 69 prior to declining in those aged 70 or more [4].

Risk factors

Bladder stones, primarily composed of ammonium acid urate, were historically more common in children in resource-poor, predominantly agricultural areas. As diets became richer in animal products, the incidence of bladder stones decreased, perhaps due to the impact of greater intake of phosphorus in the diet [5]. Bladder stones are now very uncommon in the United States except in instances of lower urinary tract obstruction due to prostatic hypertrophy, leading to, most often, uric acid stones.

Upper urinary tract stones (in the kidney or ureter) may be considered a disease of relative prosperity. The incidence of stones decreased during both world wars in Europe and Japan and increased after the wars ended. It is speculated that a return to a more animal protein–rich diet may explain the association [5].

In the current day, it is well understood that nutritional factors play a role in the development of kidney stones. There is a wealth of dietary data from prospective population studies which has helped elucidate which dietary habits increase risk of an incident kidney stone. The Health Professionals Follow-up Study (HPFS) includes over 45,000 men ages 40–75, while the Nurses' Health Study (NHS) I and II include roughly 100,000 women in each study, aged 30–55, and 25–42, respectively. Information on diet, medical history, and medications was collected at study initiation. Those with a prior history of kidney stones were excluded from data analysis.

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Putative dietary promoters of calcium-containing stones include high sodium intake (seen in women, not men), high protein intake (seen in men but not women), and high sucrose intake (seen in women, not men). Putative dietary inhibitors of calcium-containing stones include higher potassium intake (both men and women), high magnesium intake, high fiber intake, and high vitamin B6 intake (in women, not men) [6]. The reasons why some of these dietary factors are significant in one sex and not the other are not known.

Higher fluid intake and a diet more consistent with the Dietary Approaches to Stop Hypertension (DASH) study, high intake of fruits, vegetables, nuts and legumes, low-fat dairy, whole grains, low intake of sodium, sweetened beverages, and red and processed meats decrease the risk of incident kidney stones [7]. In postmenopausal women, greater intake of fiber, fruits, and vegetables was associated with a decreased risk of incident kidney stones [8]. Caffeinated coffee, decaffeinated coffee, tea, beer, and wine decreased the risk of incident stones, while apple juice and grapefruit juice increased the risk [9].

Being overweight or obese increases the risk for a kidney stone in both men and women [2]. Diabetes, gout, and lower household income also increased the risk of developing a kidney stone [2]. Stones are more common in warmer climates, where transdermal water losses are stimulated by ambient heat, leading to lower urine volume and more concentrated solute excretion [10].

Certain occupations may also increase the risk of kidney stones. For example, taxi cab drivers [11], who have infrequent access to rest rooms, are at higher risk, as are those who work in hot environments or with infrequent access to fluids, such as surgeons and nurses.

An initial evaluation of a kidney stone patient should include a detailed medical history. Bowel disease leading to chronic diarrhea and malabsorption increases the risk of kidney stones. Bariatric surgery (Roux-en-Y gastric bypass), small bowel resection, and ileostomy will increase risk. Systemic diseases that increase urine or serum calcium will also increase risk and include primary hyperparathyroidism and sarcoidosis. Carbonic anhydrase inhibitors, including topiramate, will increase risk by reducing urine citrate excretion.

The gut microbiome

Nontraditional risk factors for stones include consideration of the patient's microbiome, the environment created by the microorganisms associated with the patient. For example, *Oxalobacter formigenes* degrades oxalate in the intestinal tract. Patients who are colonized with this organism have fewer stones and lower urinary oxalate levels [12]. Antibiotics are known to affect the prevalence of this organism in the human intestinal tract [13]. Antibiotic use is also associated with an increased risk of kidney stones [14]. Antibiotic use could affect stone risk by altering a patient's microbiome. Probiotics do not decrease urinary oxalate levels [15].

Stone formation

The urine of most individuals consuming the "Western diet" is supersaturated at least sometimes with respect to calcium and oxalate, meaning that the potential for stone formation exists in most people. However, clinical stone disease occurs in only a small subset of the population. Much work has gone into understanding how stones form in the urine. At high concentrations of calcium and oxalate, homogeneous nucleation of crystals may occur spontaneously, but these levels are not commonly observed. However, at the calcium and oxalate concentrations more typically observed, spontaneous crystal formation is less likely, and, thus, stone formation may not occur even in the presence of urine supersaturated with respect to calcium and oxalate. The key step, therefore, in the formation of a stone is the formation of the initial crystal nidus. Many years ago, Randall hypothesized that areas of apatite plaque in the renal tubule serve as a base for stone formation and development, serving as an initial nidus where stones can attach and grow. Once a nidus has formed, the potential exists for stone growth in situations where the free concentrations of oxalate and calcium exceed the solubility of calcium oxalate. Thus conditions in which increased oxalate or calcium concentration in the urine occur increase the likelihood of stone formation. Other factors, however, affect stone formation as well.

Promoters of stone formation include low urine volume, sodium, low urine pH, and urate. In contrast, other urinary components, including inorganic compounds like citrate and magnesium, or organic compounds, such as osteopontin, urinary prothrombin fragment 1, and glycosaminoglycans, serve as inhibitors to stone formation. These organic compounds are thought to adsorb to the surface of the crystal, directly inhibiting further crystal growth. In addition, small amounts of other inorganic compounds such as zinc, composing the "elementome," may be important in stone formation [16].

Stones may also be caused by contaminants in food such as silica in milk, or melamine in infant formula.

Goals for the treatment of recurrent stone formers

For patients who have already had a kidney stone, the goal of therapy is to transform the urine from one that is lithogenic to one that is undersaturated in terms of likelihood of crystal formation. Saturation is defined as the ratio of the concentration of a substance in the urine to the solubility of the substance. For example, calcium oxalate saturation can be calculated from a 24-hour urine collection by measuring the urine calcium and oxalate concentrations, and the urine pH. Commercial laboratories report urine supersaturation for most stone types using a computer program called EQUIL2 [17]. The key factors in determining supersaturation for stone types include calcium and oxalate for calcium oxalate stones, calcium phosphate and pH for calcium phosphate (apatite or brushite) stones, and urate and pH for uric acid stones.

The goal for therapy is to keep the saturation below the level at which crystal growth will occur. This level is often lower in stone formers than nonstone formers because the kidney may already contain nucleation sites (Randall's plaques or existing stones or stone fragments).

The American Urologic Association (AUA) [18], the European Association of Urology (EAU) [19], and other organizations have recently published dietary guidelines (generally expert opinion) for the management of kidney stones [20–22]. The following sections on fluid, calcium, protein, sodium, vitamin C, vitamin D, sugar, potassium, and phytate intake are specifically for calcium stone formers unless noted. At the end of each section, we give our specific recommendations for the nutrient involved.

Fluid intake for recurrent stone formers

Increasing fluid intake is an appropriate first step in management for everyone with kidney stones. It is clearly the most important therapeutic manipulation as it is highly effective, inexpensive, and safe. It is well tolerated, except for the obvious effect to increase urinary frequency, which may not be appreciated by people in certain occupations or with lower urinary tract obstruction, such as benign prostatic hypertrophy. Increasing urine volume with ingestion of water led to a reduced propensity for the crystallization of calcium oxalate [23]. Fluid intake of 2 L or more a day was shown in a randomized trial to decrease the 5-year rate of stone recurrence by more than half, from 27% to 12%. Baseline fluid intake was lower in stone formers compared to controls without stones [24]. Data from prospective cohort studies also show that higher fluid intake is associated with fewer incident stones [25]. A recent meta-analysis also found a significantly reduced risk of incident stones with high fluid consumption [26]. Both the AUA and EAU dietary guidelines address fluid intake. The AUA suggests sufficient fluid for a urine volume >2.5 L daily [18]. The EAU suggests fluid intake of 2.5–3.0 L daily, with circadian drinking of neutral pH beverages, with a goal urine output of 2.0–2.5 L daily and a urine specific gravity <1.010 [19].

Affect of the type of fluid on stone risk

Mineral water may contain calcium, magnesium, sodium, and bicarbonate. In one study, patients with kidney stones were asked to drink mineral water with varying amounts of calcium. Patients who had mineral water with the highest calcium had higher urinary calcium but lower urinary oxalate with similar calcium oxalate saturations [27]. Another study evaluated the changes in urine chemistries in subjects given a standard diet and either mineral water rich in magnesium, calcium, and bicarbonate or neutral fruit tea. Those who received the mineral water (drunk between meals) had higher urinary pH, magnesium and citrate excretion, and higher calcium excretion. The relative supersaturation of calcium oxalate did not change [28]. In the follow-up phase of the study, subjects told to drink 1.4 L of mineral water daily had improved calcium oxalate saturations primarily due to a higher urine volume. High-bicarbonate mineral water increased urinary pH and citrate [29]. However, it may also increase the activity product for calcium phosphate stones [30].

In general, water with magnesium, modest amounts of calcium (30 mmol/L or less), and alkali (bicarbonate) may be beneficial for patients with calcium oxalate or uric acid stones and has not been shown to be deleterious for stone formation.

Caffeine, coffee, and tea

Caffeine intake causes both natriuresis and diuresis [31] and leads to an increased urinary calcium, magnesium, citrate, and sodium [32]. However, ingestion of caffeine-containing beverages is associated with a lower risk of incident kidney stones in the HPFS, and NHS I and NHS II cohorts [33]. The intake of caffeine was associated with higher urine volume, calcium, potassium, and lower urine oxalate and supersaturation for calcium oxalate and uric acid [33]. A decreased incidence of stones with increasing coffee intake was also seen in the Vietnam Era Twin registry, with those who drank five or more cups of coffee a day half as likely to develop kidney stones as those who did not drink coffee [34].

Black tea has more caffeine and more oxalate [35] than green or herbal tea. In observational studies, tea drinking is generally associated with a decreased risk of kidney stones [36–38], although one smaller study from northern China found the opposite association [39]. Massively excessive intake of tea has occasionally been reported to lead to oxalate nephropathy.

Beverages containing citrate

Citrate has a dual role in the management of kidney stones. Citrate in the urine complexes with calcium, reducing relative saturation and the risk of stone formation. It also inhibits crystals clumping together, an effect called aggregation, and as the size of the crystals increases, citrate inhibits their agglomeration. Importantly these latter effects decreasing the risk of stone formation are not reflected in the supersaturation equations used to determine the risk of crystallization. Citrate is also used to alkalinize the urine. Dietary citrate is metabolized by the liver and kidney and consumes a proton, the equivalent of generating bicarbonate. The resulting alkalosis inhibits proximal tubule citrate reabsorption by the sodium dicarboxylate cotransporter, leading to more urinary citrate and a higher urine pH. Potassium citrate or potassium bicarbonate is, thus, often prescribed, particularly for the treatment of calcium oxalate, uric acid, cystine stones, or for calcium phosphate stones in distal renal tubular acidosis (RTA). Thus most recurrent stone formers benefit from high citrate intake. Achieving this can be difficult as medication is often prescribed two to three times daily (for a daily dose of 30−60 mEq) and compliance can be a major issue. Eating less animal protein yields less protons, which has the same effect to increase urine citrate as increasing ingestion of fruits and vegetables.

Most studies demonstrate some increase in urine pH and citrate content with ingestion of orange juice, lemon juice, lemonade, high-citrate sodas, and powdered beverages and have been extensively reviewed [40,41]. Table 36.1 shows a summary of alkali content (usually citrate and/or malate) content of various beverages.

Clearly, the volumes required of any of the beverages listed earlier would not be feasible to drink daily on a routine basis. We, therefore, consider these beverages as adjuncts to therapy and not replacement for citrate or bicarbonate therapy. In general, we suggest sugar-free Crystal Light, or orange juice for patients with low urinary citrate or low urinary pH who want a sweetened beverage. Pineapple or melon juice (300 mL of blended fruit with 85 mL of water) may be attractive alternatives. Although non-colas (sodas) generally have a high citrate content, both sugar sweetened and artificially sweetened non-colas are associated with an increased risk of kidney stones based on population cohort studies [36] and, therefore, are not recommended. The additional calories of these beverages are also undesirable.

Lemon juice contains a high amount of citric acid which does not generate net bicarbonate when metabolized and, therefore, is not expected to have much benefit and is not recommended. However, citrus juices also contain other citrate salts which do yield net alkali. With a higher pH, orange juice contains more potassium citrate and less citric acid than lemon juice and, therefore, has greater utility for stone prevention [46]. Multiple studies have explored the role of lemonade in the management of hypocitraturic stone disease. Two studies that showed benefit did not specifically control for the type or amount of sweetener used [47,48]. In another study, lemonade showed no benefit to increase to increase urinary citrate or pH but did improve urinary output [49]. Another study compared lemonade therapy to lemonade and potassium citrate and found that the combination was more effective in increasing urinary citrate [50].

Consumption of sugar sweetened colas, non-colas, and punch are all associated with an increased incidence of kidney stones [36].

TABLE 36.1 Citrate equivalents of various beverages [42−45].

Beverage	Citrate (mmol/L)	Amount 30 mEq of alkali (L)	Amount 60 mEq of alkali (L)
Orange juice (citrate and malate)	36	0.83	1.6
Lemon juice	48	0.63	1.25
Lemonade[a]	17−39	1.07	2.1
Pineapple juice	42	0.71	1.4
Coconut water (citrate and malate)	14	2.14	4.28
Sodas with citrate[b]	8−11	3.16	6.3
Crystal Light	38	0.8	1.6
Melon (citrate and malate)	46.7	0.6	1.3

[a] *Most of the citrate in lemon juice is in the form of citric acid, limiting the net alkali load.*

[b] *Sodas with high citrate are generally orange or citrus flavored: 7Up, Orange, Sierra Mist, Ginger Ale.*

Adapted from Patel RM, Jiang P, Asplin J, Granja I, Capretz T, Osann K, et al. Coconut water: an unexpected source of urinary citrate. BioMed Res Int 2018;2018:3061742; Haleblian GE, Leitao VA, Pierre SA, Robinson MR, Albala DM, Ribeiro AA, et al. Assessment of citrate concentrations in citrus fruit-based juices and beverages: implications for management of hypocitraturic nephrolithiasis. J Endourol 2008;22(6):1359−66; Eisner BH, Asplin JR, Goldfarb DS, Ahmad A, Stoller ML. Citrate, malate and alkali content in commonly consumed diet sodas: implications for nephrolithiasis treatment. J Urol 2010;183(6):2419−23; Baia Lda C, Baxmann AC, Moreira SR, Holmes RP, Heilberg IP. Noncitrus alkaline fruit: a dietary alternative for the treatment of hypocitraturic stone formers. J Endourol 2012;26(9):1221−6.

Grapefruit juice intake was noted in population cohort studies to increase risk of incident kidney stones [9,51]; however, a short-term study showed no increase in lithogenicity with grapefruit juice ingestion [52]. A recent metaanalysis found that citrus-based products increase urinary citrate significantly [53].

Calcium intake

Calcium absorption, calcium–protein binding in blood (only unbound calcium is filtered), and the renal handling of calcium affect the amount of calcium in the urine. Intestinal calcium absorption is regulated by 1,25-vitamin D. Calcium stone formers are known to have elevated 1,25-vitamin D levels [54], consistent with high urinary calcium levels being the most common metabolic abnormality in stone formers. Calcium reabsorption from the nephron is influenced by sodium. Volume depletion and low urinary sodium lead to increased calcium uptake by the kidney. Sodium excess will increase calcium excretion. Limiting calcium intake will decrease urinary calcium but will not decrease the risk of recurrent stones.

This effect was shown in a clinical trial by Borghi's group in which Italian men with recurrent calcium-containing stones, who had urine calcium excretion greater than 300 mg/d, were randomized to a diet that contained a "normal" amount of calcium (30 mmol or 1200 mg), low protein (52 g a day) and low salt (50 mmol of sodium) versus low calcium (10 mmol, or 400 mg), low protein, and low salt [55]. Both arms were advised regarding the restriction of oxalate intake. The "normal" calcium-containing diet is actually a relatively high calcium intake in most current urban populations. Compared with the low-calcium diet, the higher calcium diet was associated with nearly half as many recurrent stones after 5 years (Fig. 36.1). Based on the findings of population-based studies showing lower incidence of stones with higher calcium intake [25] and review of existing clinical trials, both the AUA [18] and the EAU [19] recommend dietary calcium intake 1000–1200 mg daily, limited sodium, and limited animal protein for patients with calcium-containing stones. A recent Cochrane review also concluded that there was a benefit from a normal-calcium, low-protein, and low-salt diet for stone patients with higher urine calcium excretion [56].

The effect of increasing calcium intake is attributed to the binding of oxalate in the intestinal lumen, limiting its absorption. Data from the HPFS, NHS I and II show only a slight increase in urinary calcium with increasing calcium intake about 18 mg/d more in those from the highest quintile of calcium intake versus those from the lowest [57]. The inverse relationship between increased calcium intake and decreased urinary oxalate has also been demonstrated [58]; however, a retrospective analysis of Swiss kidney stone formers showed that a diet low in sodium and calcium did not increase urinary oxalate [59].

The Women's Health Initiative examined the role of calcium and vitamin D supplementation for the prevention of fractures in healthy postmenopausal women. Daily calcium (1000 mg of calcium carbonate) and vitamin D (400 IU of D3) resulted in a small but significant improvement in hip bone mineral density but did not reduce hip fracture. However, there was an increased incidence of kidney stones in the group receiving supplementation [60]. A subsequent analysis of these data showed a modest increase in the risk of cardiovascular events associated with the use of calcium supplements [61]; however, this topic remains controversial [62]. The USPSTF recommends against 25-OH vitamin D supplementation for the prevention of fractures; however, calcium and vitamin D supplements are still important in

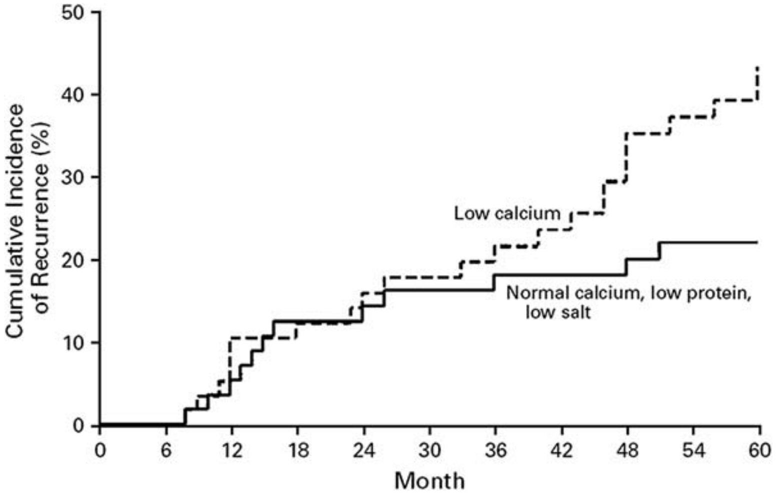

FIGURE 36.1 Kaplan–Meier estimates of the cumulative incidence of recurrent stones, according to the assigned diet.

the treatment of bone disease [63,64]. Urinary calcium concentration and, therefore, the risk of kidney stone formation could be effectively mitigated in patients taking 500 mg/d in calcium supplements if the urine volume was greater than 2 L daily [65].

Therefore we recommend 800 IU of vitamin D3, and 1200 mg of calcium in the form of calcium-rich foods, not supplements, along with fluid intake of 2–3 L daily, for our stone patients who are postmenopausal or have been diagnosed with osteopenia or osteoporosis. In those lactose-intolerant patients, we recommend lactose-free dairy products and calcium-fortified orange juice. If calcium supplements are absolutely necessary, we prefer calcium citrate, which may have a slightly more favorable effect on urinary supersaturation [66]. In addition, calcium citrate should be taken with or shortly after meals in order to bind oxalate in the intestinal lumen and reduce its absorption. The effect of calcium supplementation on urinary calcium and supersaturations for calcium oxalate and calcium phosphate should also be monitored. Recent nontrial data demonstrate that bisphosphonates may reduce stone formation, so that medical therapy of reduced bone density may be preferred therapy for stone formers [67].

Vitamin D intake

25-OH vitamin D deficiency is common in stone formers (roughly 30%) and is associated with higher parathyroid hormone levels [68]. However, 25-OH vitamin D status (levels between 20 and 100 ng/mL) or 25-OH vitamin D intake (either dietary or supplemental) was not associated with kidney stone incidence [69,70], and 25-OH vitamin D levels were not associated with an increased risk of incident kidney stones [54]. Since 25-OH vitamin D deficiency is common, we and others [71] recommend repletion of vitamin D in patients with deficiency and appropriate dietary intake of vitamin D. Short-term repletion studies show no increase in urinary calcium excretion or supersaturation for calcium oxalate or calcium phosphate in known stone formers [72] and longer term studies show no increase in stone prevalence [73].

Vitamin C intake

Vitamin C (ascorbic acid) is metabolized to oxalate and, therefore, can lead to higher urinary oxalate levels. Two independent groups have shown that vitamin C intake is associated with an increased risk of kidney stones in men [74,75]. It is interesting to note that there was no increase in the risk of incident stones with multivitamin intake [75]. Based on these results, we encourage our stone patients to get vitamin C through dietary sources (citrus fruit intake) but not through supplements. We are neutral on the use of a non-calcium containing multivitamin.

Zinc intake

Decreased zinc intake is associated with an increased incidence of calcium-containing kidney stones in adolescents [76] and, therefore, appropriate dietary intake should be encouraged.

Protein intake

Rats fed a high-protein diet have higher urinary calcium excretion, higher urinary volumes, and lower urinary citrate. There was significant bone resorption in the higher protein group suggesting that bone loss was contributing to increased urinary calcium excretion [77]. In normal men a high-protein diet (2 g/kg/d) led to increased urinary calcium, urinary uric acid, and decreased urinary citrate [78]. Interestingly a high-sodium diet also led to increased urinary calcium and decreased urinary citrate, and the changes became more pronounced when the high-sodium and high-protein diets were combined [78]. A similar study in healthy women also showed an association of increased urinary calcium and net acid excretion with higher protein intake [79]. Epidemiologic data from the HPFS study show a modest increase in the risk of incident kidney stones with increased nondairy protein intake, but this was not found in the NHS I or NHS II studies [80]. This negative result may be partly due to the lower protein intake in these studies with the highest quintiles having only 64–73 g of protein daily. This same study showed a decrease in the risk of incident kidney stones in younger women (NHS II) with increased intake of dairy protein. A recent study from China showed an increase in incident stones with higher animal protein and nondairy animal protein intake but not with plant protein intake [81].

A low-carbohydrate, high-protein diet, now a common weight-loss strategy, increases urinary acid load and urinary calcium and decreases urinary citrate [82]. If protein intake is kept the same, a vegetarian diet decreased the risk of uric acid stones but not calcium-containing stones [83,84].

Guidance regarding optimal protein intake for kidney stone patients is lacking as two randomized trials failed to show a benefit for a low-protein diet [85,86].

Despite those negative trials and based on the effects of animal protein on urine chemistry, our practice is to discourage high-protein, low-carbohydrate diets, and to encourage normal protein intake (0.8–1 g/kg/d), favoring a DASH dietary approach that incorporates low-fat dairy intake.

Sugar intake

Ingestion of 100 g of glucose or sucrose led to an increase in urinary calcium excretion in both normal subjects and calcium stone formers [87]. Urinary calcium and oxalate also increase after fructose infusion [88]. Women (NHS I and NHS II) and men (HPFS) with higher fructose intake had a higher risk of incident kidney stones but other nonfructose carbohydrates were not associated with increased risk [89]. No trials have been conducted to further elucidate the role of sugars in kidney stone disease, but in general high sugar intake is discouraged.

Phytate intake

Phytate or myo-inositol hexaphosphate is found in beans, grains, nuts, and seeds. Phytate inhibits kidney stone formation by complexing with calcium and preventing crystallization. Younger women (NHS II) with higher phytate intake had a lower risk of kidney stones compared to those with lower phytate intake [90]. Urinary phytate levels are lower in stone formers compared to nonstone formers, and a diet free of phytate will decrease urinary phytate by 50% [91]. Western diets are typically low in phytate, while vegetarian diets are higher [92]. High dose of sodium phytate in patients with higher urine calcium excretion led to a decrease in urinary calcium excretion [93] but this treatment approach has not been recently studied.

Sodium intake

Low sodium intake is generally prescribed for calcium kidney stone formers (Table 36.2). High salt intake leads to mild volume overload, inhibition of the renin–angiotensin system and decreased renal sodium uptake, and, therefore, decreased passive calcium uptake resulting in higher urinary calcium. Every 100 mEq of sodium increases urine output of calcium by about 24 mg [94], which may only be clinically significant when very high quantities of sodium are chronically ingested, as typical urinary calcium excretion is about 150–250 mg daily, and sodium intake is typically 80–200 mEq daily. However, the effect of sodium intake on urinary calcium seems higher from clinical trial data.

Stone formers have higher sodium ingestion and higher urinary calcium than nonstone formers [95]. Stone formers with higher urine calcium excretion treated with mild calcium restriction (500–700 mg/d) had a decrease in urinary calcium on a low-sodium (80 mEq daily) compared to no-sodium restriction [96]. A larger, randomized controlled study showed that stone formers in idiopathic higher urine calcium excretion on a low-salt diet had significantly lower urinary calcium than those on the control diet (water therapy alone) [97] with a reduction of about 64 mg of calcium for every 100-mEq decrease in sodium. Successful restriction of sodium intake was considered an important reason for the success of the diet with higher calcium intake described earlier (PMID: https://pubmed.ncbi.nlm.nih.gov/11784873/).

However, the reduction of sodium intake will not be beneficial to stone formers with a tendency toward volume depletion (from chronic diarrhea or another bowel pathology). An elegant study showed that calcium stone formers with hypocitraturia benefited from sodium chloride intake with an increase in urine volume and a decrease in the supersaturation for calcium oxalate stones [98]. Since lowering urine calcium excretion is generally advisable, regardless of how high it may be, advising less salt intake is usually appropriate.

Dietary management of idiopathic hyperoxaluria

Hyperoxaluria can also occur as a byproduct of excessive dietary intake, although this is usually not the primary cause of oxalate-containing stones [99]. Oxalate intake does not differ between stone and nonstone formers [99]. Although oxalate is found in a variety of foods of plant origin such as nuts, cocoa, and dark leafy greens, the most common sources of oxalate in an American diet tend to be spinach (cooked and raw), potatoes, and cold cereals. Low calcium intake is typically associated with greater oxaluria, as the absence of intestinal calcium favors oxalate absorption from the gut over oxalate precipitation and excretion from the gut. The risk of incident stones was higher in men with high oxalate and low calcium intake ($P = .08$ for the interaction) [99].

In normal subjects the elimination of fruit and vegetables led to decreased excretion of urinary potassium, magnesium, citrate, and oxalate and increased the excretion of calcium and ammonium [100]. Although high oxalate diets can slightly increase the risk of an incident kidney stone [99] and low-oxalate diets reduce urinary oxalate [15], the concern is that asking patients to restrict some high oxalate foods may have unintended negative consequences. An elegant study by Noori et al. evaluated the 24-hour urine profiles of patients with calcium oxalate stones and hyperoxaluria who were placed on either a low-oxalate or

TABLE 36.2 Comparison of American Urologic Association (AUA), European Association of Urology (EAU), and Canadian Urology Association (CUA) guidelines for dietary management of metabolic risks for kidney stones.

Dietary Component	**AUA**	**EAU**	**CUA**
Fluid	All stone formers should have fluid intake that will achieve a urine volume of 2.5 L daily	Fluid intake of 2.5–3.0 L/d Circadian drinking Neutral pH beverages Goal urine output of 2.0–2.5 L/daily Goal specific gravity (SG) <1.010	All stone formers should be counseled to achieve a daily urine output of 2.5 L
Calcium	Patients with calcium stones and high urinary calcium should limit sodium intake and consume 1000–1200 mg daily of dietary calcium	Normal calcium content (1–1.2 g/d)	The goal of dietary intake should be 1000–1200 mg/d Should calcium supplementation in a patient with calcium oxalate stone disease be required, calcium supplementation should be taken at mealtimes
Vitamin D	None	None	In calcium oxalate stone formers with documented vitamin D deficiency, repletion is appropriate but monitoring for higher urine calcium excretion is suggested
Oxalate	Patients with calcium oxalate stones and high urinary oxalate should limit the intake of oxalate-rich foods and maintain normal calcium consumption	If a 24-h urine shows hyperoxaluria, oxalate should be restricted	Patients with calcium stones and hyperoxaluria should have moderate calcium and oxalate intake
Protein	Specific restrictions only if uric acid, low citrate in 24-h urine, or with cystine stones	Limited animal protein 0.8–1.0 g/kg/d	In patients with recurrent calcium oxalate or uric acid nephrolithiasis moderation of animal protein intake and avoidance of purine rich foods is suggested
Sodium	<100 mEq or 2300 mg daily	Limited sodium chloride (4–5 g/d)	Patients with recurrent calcium nephrolithiasis should aim for sodium intake of 1500 mg daily not to exceed 2300 mg daily
Fruits and vegetables		Balanced diet rich in fruits and vegetables	A diet high in fiber, fruits, and vegetables may offer a small protective effect against stone formation
Vitamin C	None	None	Vitamin C supplementation of >1000 mg daily is not recommended due to the associated risk of hyperoxaluria and nephrolithiasis
Lifestyle advice	**AUA**	**EAU**	**CUA**
	None	Lifestyle advice BMI for adults: 18–25 kg/m^2 Stress limitation measures Adequate physical activity Balancing excessive fluid loss	None
Metabolic risk based on 24 h urine	**AUA**	**EAU**	**CUA**
High uric acid	Patients with uric acid stones or calcium stones with high urinary uric acid should limit nondairy animal protein	No specific dietary guideline. Medications suggested	Limit animal protein and purine intake
Low citrate	Patients with calcium stones and low urinary citrate should increase the intake of fruits and vegetables and limit nondairy animal protein	No specific dietary guideline. Alkaline citrate suggested	Eliminate reversible causes Increase citrate-rich foods
High urea		Avoid excessive intake of animal protein	
Low magnesium		Magnesium supplementation 200–400 mg/d	

Adapted from Pearle MS, Goldfarb DS, Assimos DG, Curhan G, Denu-Ciocca CJ, Matlaga BR, et al. Medical management of kidney stones: AUA guideline. J Urol 2014;192(2):316–24; Skolarikos A, Straub M, Knoll T, Sarica K, Seitz C, Petrik A, et al. Metabolic evaluation and recurrence prevention for urinary stone patients: EAU guidelines. Eur Urol 2015;67(4):750–63; Dion M, Ankawi G, Chew B, Paterson R, Sultan N, Hoddinott P, et al. CUA guideline on the evaluation and medical management of the kidney stone patient – 2016 update. Can Urol Assoc J 2016;10(11–12):E347–58.

DASH-style diet [101]. There was a trend toward higher oxalate excretion on the DASH-style diet; however, the calcium oxalate supersaturation also decreased in the DASH versus low-oxalate group, driven by an increase in urine pH, urinary magnesium, and citrate. Therefore in patients with idiopathic hyperoxaluria, we do not restrict intake of high-oxalate foods, unless we unearth an unusual excessive intake of a high-oxalate food such as rhubarb or peanut butter. Instead we encourage good dietary calcium intake with meals, and high intake of fruits and vegetables. Care is different for patients with secondary hyperoxaluria, as discussed next.

Management of secondary hyperoxaluria

Intestinal disorders predispose to calcium nephrolithiasis in a variety of ways. Volume loss from frequent diarrhea results in decreased urine volume and, thus, a more concentrated urine [102]. Similarly, the systemic acidemia that results from stool bicarbonate losses leads to hypocitraturia and a lower urine pH, important risk factors for calcium stones [102]. Acidemia may also drive liberation of bone calcium, leading to an increase in urine calcium (and lower bone mineral density).

Enteric (secondary) hyperoxaluria, a complication of some intestinal disorders, is commonly observed in fat malabsorption disorders such as Crohn's disease, short bowel syndrome, in intestinal bypass procedures done for obesity [103], and with treatment with obesity drugs such as orlistat (which induces fat malabsorption). Calcium normally serves to bind oxalate in the gut and to prevent its absorption. It is believed that malabsorbed fat adsorbs calcium in the gut. The reduction in free calcium caused by fat malabsorption in these disorders leads to a significant increase in oxalate absorption. The colon is the major site of oxalate absorption, where bile salts also have an effect to increase oxalate absorption [104].

Avoidance of a high-fat, high-oxalate diet is recommended for the treatment of secondary hyperoxaluria. In addition, calcium supplements are recommended with meals, and cholestyramine has been recommended to bind excess fatty acids as well. Given that the hyperoxaluria in these disorders has been associated not just with nephrolithiasis, but also acute and chronic oxalate nephropathy and occasionally end-stage kidney disease (ESKD), therapy directed at hyperoxaluria must be aggressive in these circumstances. Oral enzyme therapy that degrades oxalate may be beneficial [105].

The AUA [18], EAU [19], and Canadian Urology Association [22] all published dietary guidelines for the management of kidney stones. These papers represent a major advancement in the field as for the first time there is expert consensus on best practices. A summary of the major guidelines regarding dietary intake are shown in Table 36.2. All agree on appropriate fluid, calcium, sodium, and oxalate intake. Some of the associations discuss other specific aspects such as lifestyle (important given the association of diabetes and obesity with kidney stones), vitamin C, vitamin D, and magnesium intake.

Uric acid stones

Low urine pH is the most common cause of uric acid stones [106]. Uric acid stone formers have a higher incidence of diabetes or glucose intolerance and less urinary ammonium resulting in hypocitraturia and low urine pH. Dietary management focuses on citrate replacement, appropriate fluid intake, and avoidance of excess protein intake. Given the highly positive effects of citrate supplementation, no randomized trials of diet for the prevention of uric acid stones have been performed. Protein restriction leads to two potential effects. Most importantly, it may lead to an increase in urine pH, reducing uric acid supersaturation. Second, it reduces uricosuria. However, reducing uricosuria is not likely to be useful if an "unduly acid urine pH" is not corrected.

Cystine stones

Patients with this genetic disorder resulting in a defect in proximal tubular uptake of cystine, ornithine, lysine, and arginine are at risk of forming cystine stones. Cystine is relatively insoluble in urine, particularly at low pH. The goals of therapy for cystine stones include alkalinizing the urine to increase cystine solubility, reducing the concentration of cystine in the urine below the threshold for precipitation (generally about 243 mg/L or 1 mmol/L) by increasing fluid intake, and maintaining cysteine in a soluble, monomeric state. No clinical trials of dietary manipulation for the prevention of cystine stones have been performed. However, we advise two prescriptions in order to change urine chemistry: restriction of animal protein intake and of sodium intake. Animal protein is a source of protons so that reducing protein intake is expected to increase urine pH and reduce the dose of potassium citrate supplementation required to achieve a higher urine pH. Protein intake is also a source of methionine, a precursor of cystine, and of cystine itself. A low-sodium diet can reduce urinary cystine excretion [107]. As with other stones, higher urine output has been shown to reduce the recurrence of cystine stones [108].

Special considerations for stone formers

Nephrolithiasis is associated with a twofold increase risk of chronic kidney disease (CKD) and ESKD independent of other known CKD risk factors [109]. Some of the explanations may be patient-specific. For example, patients with the metabolic syndrome, diabetes mellitus, or hypertension are predisposed to nephrolithiasis as well as CKD. Patients with anatomic urinary tract abnormalities that predispose to stone formation may also be predisposed to renal disease, and those with infection stones may develop renal scarring due to chronic infection.

Recently, a large cohort study demonstrated that patients with nephrolithiasis have an approximately 18% increased risk of coronary artery disease (CAD) compared to nonstone formers [110]. The effect was more pronounced in women [HR of 1.18 (1.08−1.28) in NHS I and HR of 1.48 (1.23−1.78) in NHS II]. There was no association found in a cohort of men (HPFS). Alexander et al. conducted a cohort study of over 3 million members of the Alberta, Canada universal health-care system between 1997 and 2009. They found that compared to nonstone formers, stone formers had a higher risk of acute myocardial infarction, angioplasty, and coronary artery bypass surgery and a higher risk of stroke. The risk was more pronounced for younger people and for women [111]. The mechanisms underlying these associations, including lifestyle, genetics, or diet, remain to be discovered. New insights into the physiology of stone formation may illuminate the similarity of disease progression of CKD or the vascular calcification and inflammation that gives rise to CAD. The implications may be that a diet intended to prevent kidney stones may mitigate diabetes, metabolic syndrome, and high blood pressure while addressing the risk for CAD and low bone mineral density. For that reason, we also promote the US Dietary Guidelines for Americans 2015−20 which promote health in general. Although those guidelines do not specifically address kidney stones and have not been tested for that purpose, we believe that adherence to those guidelines would likely reduce stones, promote bone health, and reduce metabolic syndrome and its accompanying comorbidities (https://health.gov/dietaryguidelines/2015/guidelines/).

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CHAPTER

37

Nutrition and blood pressure

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Introduction

Hypertension is one of the most common chronic diseases. It is currently estimated that approximately 70 million people in the 45- to 75-year age group in the United States have hypertension [1]. The prevalence of hypertension appears to be increasing. Globally, 1.13 billion people were estimated to have raised blood pressure (BP) (≥140/90 mmHg) in 2015, with the increase largely occurring in low and middle-income countries due to population growth [2]. The degree of severity of high BP and hypertension has been updated and reclassified in the 2017 ACC/AHA Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults as indicated in Table 37.1 [3]. It is important to stress that normal BP is now considered <120 mmHg systolic (SBP) and <80 mmHg diastolic (DBP) (Table 37.1).

The widespread concern over the high prevalence of hypertension is due to compelling evidence that it is a major cause of morbidity and mortality [4–6] and the recognition that lifestyle plays a major role in the pathogenesis and current high prevalence of hypertension. Hence, to the extent that hypertension is caused or intensified by unhealthy lifestyles, including unhealthy diets, it should, in theory, be preventable or treatable by modifying people's behavior. Overweight and obesity, particularly visceral obesity, low birth weight, high sodium chloride intakes, and increased or reduced intake of a number of other nutrients have been associated with increased BP [7–11]. In the past several decades, overweight and obesity have increased to epidemic proportions in industrialized countries, and the prevalence of these conditions is increasing rapidly in the developing world [10,12]. Worldwide, approximately 1.4 billion adults were estimated to be overweight or obese in 2005, and the number of such individuals appears to be increasing and is projected to be 1.9–3.3 billion people by 2030 [13]. Thus the effects on BP of obesity, energy intake and excessive or deficient intakes of other nutrients have become a subject of great importance. Table 37.2 lists nutritional factors that may affect BP. This chapter will review first the relationships between BP and obesity and energy intake and then relationships between BP and the intake of other nutrients.

Obesity and energy intake

Body mass and obesity

In adults a common way of describing normal or desirable body weight or increased body fat is the body mass index (BMI), which is defined as weight, in kilogram, divided by the square of the height, in meters. Normal or desirable BMI is generally considered to be 18.5–24.9 kg/m^2. Overweight is defined as a BMI of 25.0–29.9 kg/m^2, and obesity as a BMI of 30 kg/m^2 or greater. Morbid obesity has been defined as a BMI of 35.0 kg/m^2 or greater [12]. Obesity has also been classified as class I (BMI, 30–34.9 kg/m^2), class II (BMI, 35.0–39.9 kg/m^2), and class III (BMI, ≥40.0 kg/m^2) [14]. Overweight and obesity are considered to occur at a lower BMI in Asian peoples, because the direct association of BMI with increased risk for adverse cardiovascular outcomes, including hypertension, occurs at lower weights-for-height than in Caucasians [15–17]. Other, rather similar, BMI criteria for obesity have also been described.

Scientific evidence strongly links obesity with elevated BP. Obesity, by itself, appears to directly increase BP, and obese individuals are more likely to have elevated BP than nonobese subjects [10,17–19]. Even

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TABLE 37.1 Classification of blood pressure (BP) for adults.

BP classification	SBP (mmHg)		DBP (mmHg)
Normal	<120	and	<80
Elevated	120–129	and	<80
Hypertension			
Stage 1	130–139	or	80–89
Stage 2	≥140	or	≥90

This classification is based on the average of two or more properly measured, seated blood pressure readings performed on each of two or more office visits.
DBP, Diastolic blood pressure; *SBP*, systolic blood pressure.
Reprinted from the 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA guideline for the prevention, detection, evaluation, and management of high blood pressure in adults. J Am Coll Cardiol 2018;71:e127–248.

TABLE 37.2 Nutritional factors that may affect blood pressure[a].

Nutritional factor	Effect of nutritional status or increased nutrient intake on blood pressure
Obesity	Increase[b]
Energy intake	May increase
Fat intake	May increase
PUFA intake[c]	May decrease
MUFA intake[d]	May decrease
Fructose, glucose intake	Increase
Protein, certain amino acid intakes	May decrease
Sodium intake	Increase[b]
Potassium intake	Decrease
Magnesium intake	May decrease
Calcium intake	Little or no effect[e]
Dietary fiber	May decrease
Alcohol intake	Increase
Green coffee bean extract	Decrease
Regular coffee (+) or (–) caffeine	Decrease
Green, oolong, or black tea	Decrease
Dark chocolate	May decrease
Olives/olive oil (that contain MUFA and phenolic compounds)	Decrease
Low-fat liquid dairy products (milk, yogurt)	May decrease
DASH/Mediterranean/Nordic diets	Decrease

[a] *Some of the nutrients listed have been shown to either lower blood pressure or reduce the risk of developing hypertension, but the evidence that they do both is not always clear.*
[b] *Obesity and high sodium intakes have the greatest blood pressure–increasing effects.*
[c] *PUFA; polyunsaturated fatty acids.*
[d] *MUFA; monounsaturated fatty acid.*
[e] *Blood pressure effects of calcium are unclear. It is possible that calcium supplements may reduce blood pressure only in people who have low calcium intakes.*
DASH, Dietary approaches to stop hypertension.

among older adults, a higher BMI is associated with increased risk for hypertension. In a study of adult family medicine patients, the prevalence of prehypertension (SBP 120–139 mmHg; DBP 80–89 mmHg) increased significantly as the BMI rose from overweight to obese to morbidly obese [20]. A study conducted in Italy on 7907 general participants (the Longevity Check-up 7+ study) demonstrated that higher BMI was associated with increased risks of hypertension (as indicated by at least one SBP ≥ 140 mmHg, DBP ≥ 90 mmHg, or antihypertensive drug use) [19]. Adjusted odds ratios (ORs) for hypertension for people who were overweight or class I, class II, and class III obesity, as compared to those with normal weights, were 1.73, 3.38, 4.62, and 6.53, respectively [19]. A gain in BMI or in body fat is associated with an increased risk of developing hypertension [21]. In obese people a low dietary energy intake that induces weight loss reduces BP [22,23]. A randomized controlled trial that investigated the effects of bariatric surgery on BP among patients with a BMI of 30–39.9 who were receiving two or more antihypertensive drugs showed that those who received the bariatric surgery experienced a significant reduction in both BMI and in the number of antihypertensive drugs they were taking as compared to those who received medical therapy alone [24] (see also Chapter 40: Nutritional and Metabolic Management of Obesity and The Metabolic Syndrome in Patients with Chronic Kidney Disease, and Chapter 41: Bariatric Surgery and Kidney Disease). BP is correlated with both fat cell size and number [18]. Obese individuals may have larger adipocytes with altered metabolic activity that may produce bioactive molecules that predispose to hypertension (e.g., leptin, angiotensinogen, free fatty acids, and reactive oxygen species) as discussed in the following paragraphs [25–27]. Adipose tissue of obese individuals may undergo enhanced infiltration of macrophages which engender an inflammatory state, as indicated later [26].

Two other common methods of characterizing obesity are the waist circumference or the waist:hip ratio. These measurements reflect the amount of abdominal visceral fat mass that is more closely associated with the adverse effects of excess body fat. The waist circumference and waist:hip ratio are independent risk factors for the development of hypertension, diabetes mellitus, and cardiovascular and total mortality [28,29]. An abdominal (waist) circumference 102 cm or greater in men and 88 cm or greater in women is considered to indicate abdominal obesity [28]. The ratio of the circumference of the waist to the hip correlates directly with both SBP and DBP (i.e., the male fat distribution is correlated with the BP level) [9,18]. A meta-analysis of longitudinal studies demonstrated that both obesity (BMI ≥ 30 kg/m^2) and waist circumference ≥ 102/88 cm were similarly associated with the risk of developing hypertension [30]. Moreover, the combination of abdominal obesity and truncal obesity (i.e., a ratio of the subscapular to the triceps skinfold thicknesses of 2.24 or greater in men and 1.32 or greater in women) is associated with an increased risk of hypertension. The risk of hypertension associated with this altered fat distribution varies according to race and ethnicity [31], and even lower waist circumferences are associated with increased cardiovascular risk in certain Asian populations [32,33] (e.g., >87 and >83 cm in Japanese men and women, respectively [33]). These racial/ethnic differences concerning the quantity and location of body fat and hypertension are consistent with the results of several studies indicating that there is a gene–obesity interaction in the pathogenesis of hypertension in some people [34,35].

Mechanisms by which increased body fat causes high blood pressure

Overweight and obesity are associated with many physiological and metabolic changes that promote hypertension, as indicated in Table 37.3, and which have been recently reviewed [26,36–38]. One such alteration is the elevated activity of the renin–angiotensin–aldosterone system (RAAS) [18,39]. Obesity is associated with increased plasma angiotensinogen, renin, aldosterone, and angiotensin-converting enzyme (ACE) levels and urinary aldosterone [40,41]. Plasma renin activity (PRA), relative to the intake of sodium chloride, may be disproportionately high [18,23]. PRA and plasma aldosterone levels decrease when obese individuals lose weight, and this decrease is independent of changes in the sodium intake [18]. In experimental animal models, adipocytes release factors that stimulate the release of aldosterone and other compounds that may activate the mineralocorticoid receptor and promote sodium retention [42].

TABLE 37.3 Mechanisms of hypertension in obesity [398].

1. Activation of the RAAS:
    a. Increased serum angiotensinogen, renin, aldosterone, and ACE levels are found in obesity
    b. PRA, relative to sodium chloride intake, is increased in obese subjects
    c. Adipose tissue releases factors that stimulate the release of aldosterone and other mineral corticoid compounds
2. Obese individuals often have increased sodium intake
3. Activation of the SNS:
    a. Glucose ingestion increases plasma norepinephrine
    b. Obese subjects have higher supine plasma epinephrine, norepinephrine and PRA, and greater norepinephrine response to upright posture and handgrip exercise
    c. Weight loss leads to more normal plasma catecholamine levels
4. Thyroid hormone. Overeating increases triiodothyronine production. T3 increases beta-adrenaline receptors
5. Insulin resistance (causes increased renal NaCl reabsorption, SNS overactivity, proliferation of vascular smooth muscle cells)
6. Obesity-associated chronic kidney disease (e.g., from focal segmental glomerulosclerosis, diabetic nephropathy)
7. Release from adipose tissue of leptin, resistin (antagonizes insulin), proinflammatory cytokines (CRP, TNFα, IL-6, NEFAs), and reactive oxygen species. Rat studies indicate that these compounds may activate the mineralocorticoid receptor
8. Endothelin-1 (causes vasoconstriction, may impair nitric oxide synthesis capacity)
9. NEFAs Excessive nutrient intake may increase portal venous delivery of unsaturated NEFAs that are associated with increased blood pressure
10. Increased leptin levels, which may promote SNS activity
11. Low adiponectin levels in obesity. Low adiponectin is associated HTN, low nitric oxide production, and endothelial dysfunction
12. Obstructive sleep apnea (may increase SNS activity, cause endothelial dysfunction and enhance RAAS activity, and may be associated with low adiponectin levels

ACE, Angiotensin-converting enzyme; *CRP*, C-reactive protein; *HTN*, hypretension; *IL-6*, interleukin-6; *NEFA*, nonesterified fatty acids; *PRA*, plasma renin activity; *RAAS*, renin–angiotensin–aldosterone system; *SNS*, sympathetic nervous system; *TNFα*, tumor necrosis factor-alpha.

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Obese people who do not have heart failure or chronic kidney disease (CKD) and nonobese people with higher BMIs may have lower levels of serum or plasma probrain natriuretic peptide as well as the saliuretic compound, brain natriuretic peptide [38,43–46]. Subcutaneous adipose tissue in obese hypertensive individuals displays a reduced ratio of the mRNA level for the natriuretic peptide membrane receptor, guanylyl cyclase type-A, which is activated by natriuretic peptides, as compared to the mRNA level for the natriuretic peptide clearance receptor, which clears these peptides [38,43]. These data suggest that in obesity, there may be reduced synthesis of the natriuretic peptide membrane receptor and increased synthesis of the receptor that clears the natriuretic peptide from plasma. These findings may explain why the natriuretic and diuretic response to atrial natriuretic peptide may be reduced in obesity [47].

The sympathetic nervous system (SNS) activity may be increased in both the metabolic syndrome and obesity [18,23,48]. Insulin resistance with hyperinsulinemia and elevated plasma leptin, which is common in obesity, increase SNS activity [23,48–51]. Obese subjects have higher supine plasma epinephrine, norepinephrine and PRA, increased urinary norepinephrine, and a greater norepinephrine response to upright posture and isometric handgrip exercise [52]. Weight reduction in these individuals reduces these hormones to more normal plasma levels [52]. Glucose ingestion increases plasma norepinephrine and may raise plasma thyroid hormone. Overeating may enhance triiodothyronine production from thyroxine, and greater triiodothyronine levels may increase beta-adrenaline receptors [48,53]. In this regard, in a cross-sectional study, intake of sugar-sweetened beverages was directly related to SBP and DBP [54,55]. There was a direct relationship between dietary fructose and glucose and SBP and DBP in people with higher dietary sodium intakes [54]. A metaanalysis of prospective cohort studies demonstrated that intake of sugar-sweetened beverages was associated with an increased risk of incident hypertension [risk ratio, 1.12; 95% confidence interval (CI), 1.06−1.17] [55]. The PREMIER Trial (see later) also indicated that reduced intake of sugar-sweetened beverages was associated with decreased BP [56].

Obesity predisposes to obstructive sleep apnea [48,57,58]. Persons with increased episodes of apnea or hypopnea during sleep are at increased risk for developing hypertension [59]. Obstructive sleep apnea is associated with insulin resistance, increased SNS activity, endothelial dysfunction, enhanced RAAS activity, increased plasma leptin, and low serum adiponectin [48,57,60,61]. The severity of sleep apnea is related to increased activity of the RAAS [62]. These relationships may explain why obstructive sleep apnea−associated hypertension can be resistant to pharmacological therapy. When obstructive sleep apnea is treated effectively, there is commonly a reduction in SNS activity and a decrease in both daytime and nocturnal BP and in the refractoriness of hypertension to treatment [63,64]. Continuous positive airway pressure treatment of obstructive sleep apnea for 6 months tended to decrease 24-hour urinary aldosterone excretion. A greater decrease of urinary aldosterone excretion was found in the patients with the lower baseline minimum oxygen saturation levels, lower BMI, and nondipping BP patterns [62].

Obesity may also predispose to hypertension by promoting renal sodium retention through insulin resistance. Insulin promotes the intracellular transport of glucose by stimulating insulin receptor substrate-1 (IRS-1). Obesity induces IRS-1 resistance to the actions of insulin, and this appears to be a cause of the hyperglycemia and elevated insulin levels that occur in obesity. On the other hand, insulin stimulation of sodium reabsorption in the proximal tubules appears to be mediated primarily by stimulating insulin receptor substrate-2 (IRS-2) [36,65]. In isolated renal proximal tubules obtained from knockout mice for IRS-1, insulin still induces sodium reabsorption, presumably by activating IRS-2 [65]. However, insulin stimulation of sodium reabsorption is significantly reduced in knockout mice for IRS-2 [65]. Thus the high circulating levels of insulin in obesity, which is in part due to IRS-1 resistance to insulin, may overly stimulate IRS-2 activity and thereby enhance renal tubular sodium reabsorption, sodium retention, salt-sensitive hypertension, and edema. Weight loss reduces resistance to insulin [66].

Obesity increases the risk of CKD due primarily to diabetes mellitus, hypertension, and focal and segmental glomerulosclerosis. These former two conditions often lead to diabetic nephropathy and/or hypertensive nephrosclerosis [37]. As discussed in Chapters 39−41, obesity also promotes proteinuria and accelerates the progression of many types of renal disease. CKD, in turn, may predispose to sodium retention and hypertension.

Obesity may be associated with increased plasma leptin levels and resistance to leptin [48,49], abnormal plasma levels of coagulation factors, and increased reactive oxygen species, inflammation, and endothelial dysfunction which may also contribute to hypertension [25,48,67,68]. Weight loss in overweight and obese adults improves conduit and resistance artery endothelial function and reduces plasma leptin [69]. Patients deficient in leptin or the leptin receptor exhibited significantly lower SBP [70]. However, evidence, somewhat conflicting, suggests that SBP did not increase in leptin-treated patients with lipodystrophy [71]. Also, increased leptin levels may contribute to SNS activation, sodium retention, and vascular resistance [37,49,72,73]. Leptin appears to facilitate aldosterone production via the CYP11B2 enzyme expressed in adrenal cortical cells [74]. This mechanism may be more evident in women, and leptin and aldosterone may play important roles in maintaining sodium and water during pregnancy [74].

Adipose tissue releases leptin, resistin (which antagonizes the actions of insulin), such proinflammatory cytokines as tumor necrosis factor-alpha, nonesterified fatty acids (NEFA), and reactive oxygen species [36]. Studies in rats suggest that these latter compounds may activate the mineralocorticoid receptor [36]. Endothelin-1 released from adipose tissue causes vasoconstriction and may impair nitric oxide synthesis. Excessive nutrient intake may also increase portal venous delivery of NEFAs which may elevate BP (see earlier). Serum adiponectin levels are reduced in obesity, and low adiponectin is associated with low nitric oxide production, endothelial dysfunction, and hypertension [75].

It has been proposed that obesity also induces dysfunction of the microvasculature by the release from adipose tissue of inflammatory cytokines, free fatty acids, and other vasoactive compounds [76]. These processes lead to obesity-associated altered physiology and rarefaction of the microcirculation.

The consequences may be increased microvascular resistance and impaired delivery of insulin and glucose to target tissues (e.g., skeletal muscle). These disorders may result in insulin resistance, glucose intolerance, possibly salt sensitivity, and increased risk of type 2 diabetes mellitus, hypertension, and cardiovascular disease [76].

It is evident that many of the foregoing processes may work additively to promote hypertension and particularly salt-sensitive hypertension in overweight and obese people. For example, the combination of hyperreninemia, hyperaldosteronism, other compounds with mineralocorticoid-like actions, hyperinsulinemia, increased SNS activity, CKD, a propensity to retain sodium, and polyphagia with excessive sodium intake may cause sodium chloride–sensitive hypertension [37,65,77,78]. Insulin resistance also may predispose to both increased activity of the renin–angiotensin system [39] and inflammation [79]. Increased SNS activity in association with increased endothelin-1 and other factors elaborated with obesity may promote endothelial and vascular dysfunction [37]. The metabolic actions of adipocytes appear to contribute importantly to many of these processes.

Obese individuals are at increased risk for the metabolic syndrome. The Adult Treatment Panel III of the National Cholesterol Education Program defines the metabolic syndrome as the presence of at least three of the following constellation of characteristics [80,81]: an increased abdominal waist circumference (>40 inches in men; >35 inches in women), elevated BP (130/85 mmHg or greater), hypertriglyceridemia (150 mg/dL or greater), low-serum high-density lipoprotein cholesterol (<40 mg/dL in men and <50 mg/dL in women), and a fasting blood glucose of 110 mg/dL or greater. Other expert groups have defined the metabolic syndrome somewhat differently, but the essence of these other definitions of the metabolic syndrome is similar to what is described here [80].

People with the metabolic syndrome are likely to have hypertension (which is also part of the metabolic syndrome) and are prone to develop diabetes mellitus, particularly type 2. They are also at high risk for cardiovascular, cerebral-vascular, and peripheral vascular disease. Due to this association with vascular disease, some investigators have expanded the concept of the metabolic syndrome to include other cardiovascular risk factors, and particularly those risk factors associated with inflammation [82], CKD, as well as cardiovascular disease [7]. Emerging evidence indicates that the metabolic syndrome, which includes obesity as one of its characteristics, is also associated with the increased production of aldosterone and activation of the mineralocorticoid receptor, and that these changes may promote inflammation, oxidative stress, and insulin resistance [83]. The usefulness of the concept of the metabolic syndrome has recently been challenged, because it is argued that the hazard ratios (HRs) for morbidity and mortality associated with the metabolic syndrome may be no greater than the sum of the HRs of the individual components of the syndrome [84]. Some observers have described a direct association between hypertension and BMI, increased waist circumference, obesity, weight gain, diabetes mellitus, and nephrolithiasis [85–89].

Both calcium oxalate and uric acid stones, as well as elevated serum urate and altered urate metabolism, are associated with an increased prevalence of obesity, diabetes mellitus, and hypertension [85–88]. Several causes for these interrelationships have been proposed [86,88,90], but the exact mechanisms are not clearly established (EST). People who are psychologically depressed are also at greater risk for hypertension [91]. This association may be due, in part, to the greater likelihood that depressed people will have a high BMI [92]. Patients with depression are more likely to have sympathetic hyperactivity. Plasma levels of norepinephrine and its metabolite, 3-methoxy-4-hydroxyphenylglycol, were found to be higher in patients with major depression than in control patients [93]. Moreover, electroconvulsive therapy decreases plasma norepinephrine levels in parallel with the resolution of depression [94].

High energy intakes, independent of obesity, also seem to engender hypertension in obese individuals. Dornfeld and coworkers studied the BP of obese patients during and after treatment with a protein-sparing modified fast [95]. During this treatment, BP fell quickly and profoundly, even before much weight was lost. When the low-energy-formula diets were discontinued and regular foods were reintroduced into their diet, many of these individuals began to ingest excessive quantities of energy and regained weight. Interestingly, for a given body weight, the patients' SBPs and DBPs were significantly greater when these same patients were ingesting excessive energy intakes and gaining weight as compared to when they were at the same body weight but eating a calorie-deficient diet and losing weight. The excessive energy intake could be the cause of the greater BPs for a given body weight during weight gain as compared to weight loss. However, possible contributions to this elevated BP from metabolic processes associated with new fat deposition or from the excessive intake of other nutrients, such as sodium and chloride, cannot be excluded.

Among obese, normotensive individuals, short-term weight gain, weight loss, or weight gain followed by weight loss, as compared to those whose weight was stable, were associated with an increased risk of developing hypertension within 2 years [96]. A metaanalysis demonstrated that such fluctuations in body weight might be associated with an increased risk of death.

The HR for death in the group with the greatest fluctuations in body weight group was 1.45 (95% CI 1.29−1.63) compared to the reference group, although heterogeneity and publication biases were found in these analyses [97]. The reduction in BP that occurs with weight reduction does not appear to be due exclusively to a reduction in energy intake and fat mass. Obese individuals often have increased dietary sodium intake [98], which may also promote hypertension (see later). As indicated earlier, hyperinsulinemia and possibly alterations in the physiology and anatomy of the microcirculation, which are often present in obesity, tend to increase renal tubular sodium reabsorption. However, Reisin et al. provided evidence that in obese, hypertensive individuals, ingestion of low-calorie diets and weight loss, independent of a reduction in dietary sodium intake, can lower BP [22]. These investigators placed obese patients on an energy-restricted, weight-reduction diet. Each day each individual was fed an amount of sodium equal to the sodium content in his previous 24-hour urinary output. Even though the total body sodium content fell little if at all in these patients, they experienced a substantial fall in mean BP as they lost weight [22].

The foregoing considerations indicate that there are multifactorial causes for hypertension in overweight and obese people. Reduced dietary energy intake and weight loss in obese people probably reduces hypertension by a number of mechanisms. It is important to keep in mind that very obese individuals may have a falsely elevated BP when it is measured with a normal-sized BP cuff. For accurate BP measurements, the cuff size should be adjusted to the arm circumference of the patient and increased for individuals with large-arm circumferences and reduced for people with small-arm circumferences.

Excess fat in neonates and children and low birth weights

Overweight children are at increased risk for hypertension as they become older. Obese children develop substantially increased numbers of adipocytes in their bodies that persist into adulthood, and this factor is considered to contribute to the difficulty in attaining normal fat mass in obese adult patients who were obese in childhood. On the other hand, children with low birth weights are also at greater risk of developing hypertension. This latter phenomenon was observed in the Helsinki study [99]. The low birth weights are often due to maternal malnutrition or to impaired ability to deliver nutrients to the fetus; for example, due to disorders in the placenta or reduced blood flow through the umbilical artery [100]. Low birth weight children often gain excessive weight by the end of the first 10 or 15 years of life, and presumably their increased body mass may contribute to their increased risk of developing hypertension [99]. It has also been postulated that low birth weight children often have a smaller number of nephrons in their kidneys, which may predispose them to sodium chloride retention and, hence, hypertension [99]. Other metabolic derangements in low or high birth weight babies may predispose to the metabolic syndrome, obesity, and hypertension [100−103]. The finding that prenatal or perinatal exposure to certain environmental stresses, such as undernutrition or overnutrition, can be associated with the development of disorders in adulthood is now recognized as a potentially important pathogenic factor. This field of study is sometimes referred to as *the developmental origins of health and disease* [104].

Fetal undernutrition

The Dutch Famine, which led to undernutrition of mothers and newborn infants in the Netherlands near the end of World War II, is an example of the long-term effects of fetal undernutrition on the propensity for obesity and hypertension [105]. Fetuses whose mothers were subjected to prenatal famine while the fetuses were in the second and, to a lesser extent, the third trimester of pregnancy in the Netherlands between November 1944 and May 1945, tended to be born with low birth weights. They were shown to be more likely to become overweight in childhood and to have a high prevalence of obesity, hypertension, and diabetes mellitus, among other disorders, when they aged into their 50s and 60s [105].

Individual nutrients, miscellaneous substances, and blood pressure

Sodium chloride

There is abundant evidence for a direct relation between sodium chloride intake and BP [68,106−108]. Sodium chloride intake correlates directly with BP across population groups. The association of sodium chloride intake and BP increases with age, the BP level and the presence of renal insufficiency, and among individuals with a family history of hypertension. The International Study of Salt and Blood Pressure (INTERSALT) involved about 10,000 adults, aged 20−59 years old, who were evaluated at 52 centers in 32 countries. This study indicated that 24-hour urine sodium excretion was significantly and positively associated with the median SBP and DBP, the upward slope of SBP and DBP that occurs with age, and the prevalence of elevated BP [108,109]. Other cross-sectional population-based studies describe a direct relationship between 24-hour urinary sodium and SBP, even after multivariant adjustments [110]. Even in normal adults, salt intake affects extracellular volume which, in turn, can affect the risk of hypertension; a reduction of dietary salt intake from 160 to 80 mEq/day reduces their body weight and extracellular volume by 1−1.5 L [111]. The chloride salt of sodium appears to have a substantially greater effect on raising BP than does sodium bicarbonate [112].

Among individuals of similar age and BP level, the pressure response to high sodium intakes varies greatly. The BP of some individuals rises with high sodium chloride intakes, whereas in other individuals, the BP does not appear to be affected by the sodium chloride intake [113]. Sodium chloride sensitivity can be diagnosed by a reduction in BP associated with low sodium chloride intake and/or an increase in BP with sodium chloride loading. Sodium chloride resistance has been defined as no rise or fall in BP after an increase or decrease in sodium chloride intake. It has been estimated that approximately 30%−50% of hypertensive persons and a smaller percentage of nonhypertensive persons are sodium chloride−sensitive. A limitation of these studies is that the testing for sodium chloride sensitivity with salt loading is generally carried out for only a few weeks or less. It is possible that a person whose BP does not increase during several weeks of sodium chloride loading, and is, therefore, classified as sodium chloride resistant, might be predisposed to hypertension if he chronically ingests large quantities of sodium chloride for many months or years. As indicated earlier, epidemiological observations support this consideration. Moreover, people who are not determined to be sodium chloride−sensitive in these short-term studies can subsequently develop diseases that render them sodium chloride−sensitive; for example, CKD or obesity. These matters are of substantial concern because the dietary sodium intakes in many societies are quite high and also because there is a high prevalence of hypertension among adults worldwide, particularly as people age. Reduction in sodium intake may be particularly effective in lowering BP in individuals who are older, obese, African-American, possibly in those who are female, and in those who have CKD, higher SBPs, or a greater SBP response to the cold pressor test [107,114].

Several metaanalyses have examined the effects of dietary salt reduction on BP [107,115−120]. A metaanalysis of randomized controlled trials that compared low sodium chloride intake (3−6 g/day) and high sodium chloride intake (10−12 g/day) in CKD stage 1−4 patients demonstrated that SBP, DBP, and both clinic and ambulatory BPs were lower with the low sodium intakes. Moreover, urine total protein and albumin excretion were significantly lower with the low salt intakes [121]. A metaregression analysis, which investigated the magnitude of BP reduction in relation to lowering the sodium intake within the framework of a metaanalysis, was conducted in 133 randomized controlled trials. This study, which compared the effects of reduced sodium intake with usual sodium intake, demonstrated a strong, linear dose−response relationship between sodium reduction and BP reduction. This was especially evident in the individuals with a mean BP above the 75th percentile (131/78 mmHg or greater). The dose−response relationship was −7.7 (95% CI, −10.4, −5.0) mmHg/100 mmol reduction in sodium intake for SBP and −3.0 (95% CI, −4.6, −1.4) mmHg/100 mmol decrease in sodium intake for DBP [122]. It is noteworthy that some metaanalyses do not report a fall in BP with a reduction in sodium chloride intake in normotensive persons [117,120]. This discrepancy may be due to the inclusion in these latter studies of acute salt loading or salt restriction that was conducted for only short periods of time, sometimes for only 5 days. Large and abrupt reductions in salt intake can increase sympathetic tone, PRA and angiotensin II levels [118,120]. When only studies of 4 or more weeks' duration were included in the metaanalysis, modest restriction of salt intake (i.e., a reduction to 78 mmol or 4.6 g/day of NaCl) was associated with lowering of BP [120].

Simply following a “no added salt diet” may reduce SBP and DBP by an average of 12.1 and 6.8 mmHg during the day and 11.1 and 5.9 mmHg at night [123]. This “no added salt diet” is defined as no added sodium chloride to foods and no intake of salty foods; sodium chloride intake should be below 5.0 g/day with a urinary sodium excretion below 100 mEq/24 hours. An extensive Cochrane review of randomized studies of high-sodium versus low-sodium diets indicated that high-sodium diets slightly but significantly decreased SBP by −1.09 (95% CI, −1.63, −0.56) mmHg in normotensive and by −5.51 (95% CI, −6.45, −4.57) mmHg in hypertensive white people [124]. This latter metaanalysis also described highly significant increases in plasma renin, aldosterone, noradrenaline, adrenaline, cholesterol, and triglycerides with sodium restriction [124].

Obesity appears to increase the sensitivity of BP to sodium chloride intake in adolescents, possibly because of the hyperinsulinemia, hyperaldosteronism, and enhanced SNS activity that are commonly found in obese individuals [77]. Weight loss in these individuals appears to decrease their salt sensitivity. Patients with essential hypertension have higher urinary free cortisol excretion [125]. Hypertensive individuals who had higher urinary free cortisol excretion were found to have a lower reduction in SBP and mean arterial pressure in response to reduced sodium intake [125]. Moreover, baseline plasma renin concentrations, obtained at the onset of an 8-week study, were inversely related to the magnitude of salt sensitivity, whereas the baseline plasma N-terminal atrial natriuretic peptide levels correlated directly with this phenomenon [126].

There is direct evidence for a genetic link for the association between hypertension and sodium intake and possibly obesity. In people 60 years of age or older, there was a linear increase in SBP and DBP with sodium loading [127]. This increase in BP with sodium loading was greatest in individuals with isolated systolic hypertension. The change in DBP in response to sodium loading varied in accordance with the type of gene polymorphism of the angiotensinogen gene, but not with regard to polymorphisms of the ACE gene [127]. Obese hypertensives who were homozygous (TT genotype) or heterozygous (TC + CC genotype) for the T-786 endothelial nitric oxide synthase (eNOS) gene were also studied [128]. The metabolic product of this enzyme, endothelial-derived nitric oxide (NOx), is a vasodilator. The heterozygous obese hypertensive patients with the TC + CC genotype, as compared to the homogyzous TT genotype patients, had a greater increase in diastolic and mean arterial BP, and a significant decrease in renal plasma flow and glomerular filtration rate in response to sodium loading [128]. Moreover, with sodium loading, the TT genotype has a significantly greater increase in plasma NOx, whereas the TC + CC genotype had a borderline significant increase ($P = .051$) in urinary NOx excretion.

Genetic polymorphism in the Klotho gene KL involving the single nucleotide rs9536314 is also associated with salt-sensitive hypertension in hypertensive humans [129]. Hypertensive patients with this polymorphism who receive an infusion of 0.9% saline have a greater rise in SBP, DBP, and mean BP as compared to those who do not have this polymorphism. The patients with this Klotho polymorphism also demonstrated a flatter BP—natriuresis relationship. Thus with an infusion of 0.9% saline, the ratio of the increase in natriuresis to the rise in mean BP was less than in people without this genetic polymorphism. There was also an inverse relationship between serum αKlotho concentrations and the change in the mean BP after the saline infusion. These findings suggest that hypertensive patients with this gene polymorphism for Klotho not only are more likely to have salt-sensitive hypertension, but they also seem to require a higher BP to maintain the same magnitude of naturesis-induced BP increase as do people without this gene difference.

BP in individuals with stage 4 [glomerular filtration rate (GFR) 15—29 mL/min/1.73 m^2] or stage 5 (GFR < 15 mL/min/1.73 m^2) CKD may be particularly sensitive to sodium loading or volume expansion [130,131]. Shaldon reported that in a 23-year-old male with chronic renal failure who was fed a salt-restricted diet for 8 weeks, BP fell from 230/145 to 135/90 mmHg, and there was a reduction in headache, nausea, vomiting, and papilledema and an improvement in vision [132]. The reduction in BP may continue for months after the removal of body NaCl by dietary salt restriction and dialysis ultrafiltration. The authors speculate that this delayed response may be due to the decrease in nonosmotically active sodium which is possibly bound in proteoglycans and glycosaminoglycans in the interstitial matrix that lines the intimal surfaces of blood vessels [133].

A growing body of evidence suggests that high-sodium intakes may promote more rapid progression of chronic kidney failure, possibly by an increase in oxidative stress, albuminuria, and BP, and alterations in glomerular hemodynamics [133,134]. Some authorities have postulated that salt-sensitive hypertension may be caused by subtle injuries to the kidney. Such injuries may be associated with both renal microstructural and physiological abnormalities [135]. These disorders may cause an impaired ability to excrete a sodium load and the consequent development of volume expansion with attendant hypertension.

Patients whose nocturnal BP does not fall or decreases only slightly are designated as nondippers. Such patients are more likely to experience more severe terminal organ damage compared to nocturnal BP dippers. The kidneys can play an important role in determining the circadian rhythm of BP. Both sodium-restricted diets and diuretics may shift circadian BP patterns from nondipper to dipper status [136,137]. Patients with the metabolic syndrome also may be salt-sensitive in this regard; their nocturnal BP, which may not have decreased before the salt restriction, may fall after they ingest a sodium-restricted diet. The prevalence of salt-sensitive hypertension is higher in patients with the metabolic syndrome as compared to those without (70.6% vs 36.0%, $P = .017$) [138]. Patients with primary aldosteronism also tend to exhibit a nondipper pattern of nocturnal BP. Their nocturnal BP fell after they reduced their sodium chloride intake from 10—12 to 2—4 g/day [139].

Potassium

Epidemiological and clinical studies concerning potassium intake indicate that potassium supplements (e.g., 60—120 mEq/day) lower BP. But some randomized, prospective trials have yielded conflicting results. However, in a metaanalysis of 19 clinical trials involving 586 hypertensives, Cappuccio and MacGregor reported that oral potassium supplements significantly lowered both SBP and DBP by −5.9 mmHg (95% CI, −6.6 to −5.2) and by −3.4 mmHg (−4.0 to −2.8), respectively, in subjects with essential hypertension [140].

In the metaanalysis by Whelton and coworkers, potassium supplements were associated with a significant reduction in mean SBP and DBP of −3.11 mmHg (−1.91 to −4.31 mmHg) and −1.97 mmHg (−0.52 to −3.42 mmHg), respectively [141]. A more recent meta-analysis by Binia et al. found that an increase in the ratio of urinary potassium to sodium excretion as well as an absolute increase in urinary potassium per se was associated with a decrease in SBP: a −2.14-mmHg decrease in SBP (95% CI, 0.15−4.14, $P = .035$) was observed for each one-unit increase in the urinary Na/K ratio [142].

Potassium intake may lower BP by increasing renal sodium losses. Potassium deficiency, even of a mild nature, may induce renal sodium retention, increase BP and engender salt sensitivity [143−145]. Mu and associates presented evidence that supplements of potassium and calcium may prevent hypertension in adolescents by promoting urinary sodium excretion [146]. Pere and coworkers fed a high-sodium diet and administered cyclosporine A to 8-week-old spontaneously hypertensive rats [147]. The animals developed hypertension and renal injury associated with renal dopaminergic deficiency [147]. A combined dietary supplement of magnesium and potassium prevented hypertension in these rats.

An increased intake of potassium with a subsequent rise in serum potassium concentrations is associated with dephosphorylation and inactivation of the Na^+−Cl^- cotransporter in the distal convoluted tubules of the kidney [148]. The epithelial Na^+ channel−expressed downstream cannot fully reabsorb the increased sodium in the tubular fluid, and hence net sodium excretion into the urine increases. Potassium-deficient diets are particularly common in African-Americans and have been associated with the high prevalence of hypertension and sodium chloride sensitivity in these individuals.

There are a number of mechanisms by which potassium intake may lower elevated BP [149]. As indicated earlier, potassium intake may increase renal sodium excretion. Potassium may also modulate baroreflex sensitivity and directly cause vasodilation, or reduce cardiovascular reactivity to norepinephrine or angiotensin II. Potassium supplementation to Dahl rats augmented nitric oxide production and vascular dilatation [150]. Another study that investigated the effect of potassium supplementation on young Dahl rats (4 weeks of age) demonstrated that potassium supplementation inhibited sympathetic vasoconstriction rather than facilitated vasodilatory mechanisms [151]. Supplemental potassium, 217 mg/day, and magnesium, 71 mg/day, for 4 weeks increased small artery compliance and reduced BP in patients with essential hypertension [152]. Thus it has been recommended that a substantial potassium intake should be maintained to prevent or treat hypertension, particularly in subjects who are unable to reduce their sodium intake and in those who are salt-sensitive or who have a family history of hypertension [149].

Nowson and coworkers reported that a reduction in sodium intake to about 70 mmol/day and an increase in dietary potassium to 85 mmol/day could maintain a lower BP and reduce the burden of cardiovascular disease [153]. Another study investigated the effects of a low-sodium high-potassium (LNAHK) diet on the BP response to antihypertensive medications. The LNAHK diet more effectively potentiated the actions of renin−angiotensin system inhibitors than other antihypertensive medications [154]. The Dietary Reference Intakes propose that adequate potassium intake is 4.7 g (120 mmol)/day, which should lower BP and reduce the BP raising effects of sodium chloride [155]. In this regard, an increase in dietary potassium intake to 120 mmol/day abolished or suppressed the frequency or severity of salt sensitivity in normotensive African-American men to the levels found in normotensive white men [145]. Also, in a randomized, double-blind, prospective controlled trial of potassium supplementation, 80 mmol/day, or placebo for 21 days in normotensive or mildly hypertensive African-Americans ingesting a low, 32−35 mmol/day, potassium diet, the potassium supplement significantly reduced their SBP and DBP [156]. A somewhat longer term, 6-week, randomized, double-blind, placebo-controlled trial in mostly normotensive adults of European descent that provided only 24 mmol/day of supplemental KCl showed that this modest potassium dose also significantly lowered mean arterial BP, SBP, and DBP [157]. However, in persons with normal BP, the BP-lowering effectiveness of potassium supplements appears to be limited [158].

It is relevant that a recent systematic review suggests that in early CKD (stages 1−2), but not in late CKD (stages 3−5), high potassium intakes protect against or slow progression of CKD and low potassium intakes may facilitate progression [159]. Notwithstanding the BP-lowering effects of dietary potassium and the possible slowing effects of dietary potassium on CKD progression, patients with advanced CKD are advised against ingesting large amounts of potassium, because hyperkalemia can be fatal. The use of medicines that block or inhibit the renin−angiotensin−aldosterone system predispose CKD patients to hyperkalemia. These medicines, especially when given to patients with diabetic nephropathy, who may have hyporeninemia or may be resistant to renin, can render these patients exquisitely sensitive to becoming hyperkalemic with potassium supplementation.

Calcium

There is considerable controversy as to whether high calcium intakes lower BP. McCarron and coworkers conducted a series of studies suggesting that calcium supplementation lowers BP [160]. Indeed, they and others found an inverse correlation across populations and ethnic groups between the mean dietary calcium intake and BP levels [160–162]. The Nurses' Health Study initially found an inverse relationship between dietary calcium and BP after the first 4 years of follow-up [163]. With longer follow-up, no independent relationship between dietary calcium intake and BP could be demonstrated [164]. Cappuccio and coworkers carried out a metaanalysis of 23 observational studies and reported an inverse relationship between calcium intake (determined from dietary diaries and food-frequency questionnaires) and BP [165]. However, the effect was rather small, and there was evidence of publication bias and heterogeneity of data across the investigations.

Bucher and associates performed a metaanalysis of 33 randomized clinical trials of dietary calcium supplementation involving 2412 individuals with or without hypertension [166]. They described for the entire group a small but significant reduction in SBP of −1.27 mmHg (95% CI, −2.25 to −0.29 mmHg; $P = .01$) but no change in DBP (0.24 mmHg; 95% CI, −0.92–0.44 mmHg; $P = .49$). In six of these studies in which participants were classified according to whether they were hypertensive or not, there was a significant fall in SBP and DBP in the hypertensive individuals but not in the normotensives [166]. Allender and coworkers carried out a metaanalysis of 22 randomized clinical trials in 1231 individuals [167]. In this metaanalysis, calcium supplementation was associated with a statistically significant but not very clinically important reduction in SBP, −0.89 mmHg (95% CI, −3.18 to −0.18 mmHg) and no significant change in DBP, −0.18 mmHg (95% CI, −0.75 to 0.40 mmHg). Griffith et al., in a large metaanalysis on the effects of supplemental calcium on BP, reported a reduction in SBP of −1.44 mmHg (95% CI, −2.20 to −0.68, $P < .001$) and in DBP of −0.84 mmHg (95% CI, −1.44 to −0.24, $P < .001$) [168]. Subjects in these studies were given calcium supplements of 400–2000 mg/day [164–168]. Calcium supplements that resulted in a median total daily calcium intake of about 1 g/day did not affect SBP or DBP in normotensive individuals [167–169]. Another metaanalysis reported that the BP-lowering effect of calcium intake was evident only in studies where dietary calcium intake was 1000 mg/day or greater [170]. In three small studies the supplemental calcium intake diminished the rise in BP response to a high sodium intake [169,171,172].

Calcium supplements may be effective in pregnant women. A metaanalysis on the effects of calcium supplementation during pregnancy demonstrated that calcium supplements reduced the risks of high BP, preeclampsia, preterm birth, and the composite outcome of maternal death or serious morbidity. These effects of calcium supplements were especially evident in women who had been eating low-calcium diets [173]. In addition, a qualitative metaanalysis indicated that maternal calcium intake tended to be directly associated with lower BPs in the offspring, especially during the first 2 years of their lives [174].

It has been suggested that discrepancies in the published results concerning the effects of calcium intake on BP may be related to the possibility that a low-calcium diet predisposes to hypertension, whereas in individuals who are already eating adequate calcium, higher intakes of calcium have little or no BP-lowering effect [166–168]. In this regard, Pan and coworkers gave calcium supplements to individuals with mild or moderate hypertension who lived in areas of China where there is both a higher prevalence of hypertension and a high salt and low calcium content of their diet. They reported that after 35 days of treatment with calcium lactate supplements that provided 800 mg of calcium/day, there was a reduction in SBP and DBP of −4.7 ($P = .027$) and −2.2 ($P = .074$) mmHg, respectively [175]. Further studies will be needed to resolve the question of whether a BP-lowering effect of calcium is largely or entirely limited to people ingesting calcium-deficient diets. In this regard the higher calcium intake in the dietary approaches to stop hypertension (DASH) combination diet and in low-fat dairy products might contribute to the BP-lowering effects of these regimens (see DASH diet later).

Fish oil

There are two metaanalyses of controlled clinical trials examining the use of omega-3 fatty acids [176,177]. In the metaanalysis of Appel and coworkers concerning 11 trials that enrolled 728 normotensive individuals [176], omega-3 polyunsaturated fatty acids (PUFA) supplements led to a significant reduction in SBP and in DBP in only 2 and 1 of these trials, respectively. In six studies involving 291 untreated mildly hypertensive individuals, reductions in SBP and DBP were observed in two and four of the trials, respectively [176]. The weighted, pooled reductions in SBP and DBP in the normotensive individuals averaged −1.0 (95% CI, −2.0–0.0) and −0.5 (95% CI, −1.2 to +0.2) mmHg. In the trials of untreated hypertensive persons, the weighted, pooled decreases in SBP and DBP averaged −5.5 (−8.1 to −2.9) and −3.5 (−5.0 to −2.1) mmHg, respectively. The doses of omega-3

PUFA used in these studies tended to be rather high, usually 3 g/day or greater [176].

Morris et al. evaluated 31 placebo-controlled clinical trials involving 1356 subjects and showed, with fish oil use, a mean reduction in SBP of −3.0 mmHg (95% CI, −4.5, −1.5 mmHg) and in DBP of −1.5 mmHg (95% CI, −2.2, −0.8 mmHg) with a statistically significant dose−response relationship [177]. There was a dose−response relationship between fish oil dose and SBP and DBP reduction. The decrease in SBP and DBP was statistically significant in the hypertensive patients but not in the normotensive subjects, although the average fish oil dose used was slightly higher in the hypertensives (5.6 g/day) as compared to the normotensives (4.2 g/day) [177]. These metaanalyses indicate that in people who are assigned to a relatively high omega-3 fatty acid intake, there is a statistically significant reduction in BP in hypertensive individuals, and little or no effect in normotensive persons. However, a metaanalysis that examined the effects of supplemental PUFA on cardiovascular risk factors failed to demonstrate a significant reduction in either SBP or DBP in the individuals who ingested higher amounts of PUFA [178]. In a metaanalysis of cohort studies, only circulating levels of long-chain $n-3$ PUFA, in contrast to the dietary intake of fatty acids or of fish, was associated with a lower incidence of elevated BP [179].

A randomized, prospective, double-blind clinical trial, in a 2×2 design, compared the effects on BP of daily doses of $n-3$ polyunsaturated fatty acids ($n-3$ PUFA), 1200 mg, a combination of three B vitamins (5-methyl-tetrahydrofolate 560 μg, vitamin B_6 3 mg, and vitamin B_{12} 20 μg), both of these treatments combined, or placebo [180]. The $n-3$ PUFA provided eicosapentaenoic acid and docosahexaenoic acid in a 2:1 ratio. The B vitamins were given, in part, to assess the effect of lowering plasma homocysteine on BP. A total of 2501 men and women with a history of cardiovascular disease were studied for 5 years. At baseline, their mean SBP and DBP (mmHg) averaged in the low 130 and 80 s, respectively, and they received a mean of 1.7 antihypertensive medications per subject. There was no effect of the $n-3$ PUFA, the three B vitamins, or the combination of both of these supplements on SBP, DBP, or mean BP in these individuals. It is possible that a higher $n-3$ PUFA dose than was used in this trial might have been more effective.

The mechanism by which fish oil may lower BP in hypertensive patients is not clear. It may be related to enhanced elaboration of prostaglandins which, in turn, may increase sodium and water excretion, promote vasodilation, and/or inhibit the release of thromboxane (a vasoconstrictor). Also, it is possible that prostaglandins may regulate renin release or decrease responsiveness to vasopressor hormones. $n-3$ PUFA might inhibit the beta-adrenergic system or activate eNOS [179,181−183]. The preponderance of studies with fish oil was of short duration (<3 months). Longer term studies will be necessary to determine whether fish oil has a sustained antihypertensive effect in hypertensive persons and also to assess the optimal fish oil dose for BP lowering. There are a number of side effects with fish oil intake, including most commonly eructation and a bad or fishy taste [176,177]. It is worth considering that the higher percentage of polyunsaturated fatty acids in the DASH combination diet may also contribute to the reduced BP with this diet (see later).

Olives, olive oil

Olives and olive oil are key ingredients of the Mediterranean diet and are thought to contribute to the BP-lowering effect of the diet. Olive oil contains substantial amounts of monounsaturated fatty acids (MUFAs) and phenolic compounds, both of which have been associated with a reduction in BP [184]. The effect of MUFA on BP has been investigated in observational and interventional studies. A prospective observational study (the European Prospective Investigation into Cancer and Nutrition study) conducted in Greece, and nine other European countries investigated the association between dietary, biological, lifestyle, and environmental factors and the etiology of cancer and other chronic diseases [185,186]. The results indicated that the amount of olive oil intake and the ratio of MUFA to saturated fatty acids in the diet were each significantly associated with lower SBP ($P < .001$ for each relationship) and DBP ($P < .001$ for each relationship) [187].

A randomized crossover trial investigated the effects on BP of a diet enriched with MUFA [provided as extra-virgin olive oil (EVOO)] and PUFA (provided as sunflower oil) [188]. Total 23 hypertensive patients with BPs <165/104 mmHg and without end-organ damage were assigned to either an MUFA-rich or a PUFA-rich diet for 6 months. The diets were similar with regard to the daily content of protein, carbohydrates, total and saturated lipids, cholesterol, and fiber and differed only in the amounts of MUFA and PUFA. After eating one diet for the first 6 months, the participants were instructed to ingest the other diet for 6 more months. The ratios of the quantity of MUFA to PUFA in the MUFA and PUFA diets were 5.7 ± 2.6 (mean ± SD) and 1.1 ± 0.6, respectively. At the end of each study period, the participants allocated to the MUFA diet, as compared to the PUFA diet, exhibited significantly lower SBP (127 ± SD 14 vs 135 ± 13 mmHg, $P < .05$) and in DBP (84 ± 8 vs 90 ± 8 mmHg, $P < .01$). BP was controlled in eight participants without antihypertensive medications during the MUFA diet, but in no participant during the PUFA diet. Moreover, the daily dosage of antihypertensive medications was significantly reduced during the MUFA diet, by 48% versus by only 4% during the PUFA diet (MUFA vs PUFA, $P = .005$) [188].

The observational Chicago Western Electric Study analyzed, in a cohort of 1714 men, the relationship of the dietary intake of a large number of nutrients to the annual changes in SBP and DBP [189]. Dietary nutrient intake was analyzed in detail on two occasions separated by 1 year at the beginning of the study, and participants were followed for up to 8 years. When analyzed individually, MUFA intake, expressed as percent of total calorie intake, was positively related to changes in SBP and DBP during this multiyear period of observation. PUFA intake, expressed as a percent of total saturated fatty acids, was positively only related to changes in DBP. However, when analyzed as part of a composite of the other nutrient intakes that were examined, almost all of these associations disappeared. The cause of the difference between these findings and the other studies of MUFA reported earlier may be the source of MUFA; in the United States and Northern Europe, the main source of MUFA is meat, and the amount of MUFA intake is highly correlated with the intake of saturated fatty acids [190]. The study design, in which nutrient intake was only assessed twice in each participant, who was followed for up to 8 years, may also limit the reliability of the findings. Please also refer to the "Effect of dietary sources of fuel on blood pressure" section.

The relationship to BP to another class of ingredients in olive oil, phenolic compounds, has also been investigated. A network metaanalysis investigated the effects of different types of olive oil on serum lipid profiles and BP [191]. The types of olive oil investigated, which were refined olive oil, mixed olive oil, low-phenolic (extra) virgin olive oil, and high phenolic (extra) virgin olive oil, contained different quantities of phenolic compounds. Total 13 randomized controlled trials involving 611 mainly healthy participants were included in this metaanalysis. The duration of treatment in these trials lasted from 3 to 12 weeks. The metaanalysis indicated that SBP, but not DBP, was significantly lower when participants ingested olive oil preparations with higher as compared to smaller quantities of phenolic compounds. The participants taking the low-phenolic (extra) virgin olive oil, which contained <200 mg phenolic compounds/kg of olive oil, as compared to the participants taking refined olive oil, from which most bioactive and antioxidant compounds, such as polyphenols and tocopherols, were removed during the refining process, demonstrated a significantly lower SBP (mean difference between the two groups, −2.87 mmHg; 95% CI, −5.39, −0.35). The group taking high phenolic (extra) virgin olive oil which contained 200 mg or more of phenolic compounds per kg olive oil manifested a nonsignificant tendency toward a reduction in SBP as compared to the participants taking the refined olive oil (mean difference, −2.99 mmHg; 95% CI, −6.12, 0.15). Moreover, the metaanalysis indicated that a daily dose of 5 or more mg/day of phenolic compounds in olive oil was associated with a significantly lower SBP (mean difference, −2.91 mmHg; 95% CI, −5.04, −0.79) as compared to a daily intake of <1 mg/day of phenolic compounds [191].

Another metaanalysis of eight randomized controlled trials investigated the differences in cardiovascular biomarkers between high- and low phenolic olive oil [192]. SBP was significantly lower in the group receiving high phenolic olive oil (mean difference, −0.52; 95% CI, −0.77, −0.27; $P < .01$) as compared to the group taking low phenolic olive oil, whereas DBP was not different between the two groups (mean difference, −0.20; 95% CI, −1.01, 0.62; $P = .64$). A randomized crossover trial investigated the effects of polyphenols in extra-virgin olive oil on BP [193]. The study recruited 24 young women with high-normal BP or stage 1 essential hypertension (SBP of 120−159 and DBP of 80−99 mmHg). They were fed both types of olive oil in a Mediterranean diet for 2 months each in a randomized crossover manner separated by a 4-week washout period. The participants were instructed to consume each day 60 mL of either polyphenol-rich or polyphenol-free olive oil; 60 mL of polyphenol-rich olive oil group provided about 30 mg/day of polyphenols. Both SBP and DBP significantly decreased from baseline with the polyphenol-rich olive oil. Changes in SBP were −7.91 ± SD 9.51 mmHg and −1.65 ± 8.22 mmHg ($P < .001$) for the polyphenol-rich and polyphenol-free olive oil, respectively. DBP decreased by −6.65 ± 6.63 and −2.17 ± 7.24 mmHg ($P < .001$) for polyphenol-rich and free olive oil, respectively. The magnitude of decrease in SBP and DBP was significantly greater in patients with higher baseline BP ($P < .001$) [193].

The foregoing data indicate that phenolic compounds, polyphenol-rich olive oil, and possibly MUFA are ingredients in olives that may lower SBP and DBP in people with mildly elevated BP.

Magnesium

Extracellular and intracellular magnesium ions inhibit calcium flux via the L-type Ca^{2+} channels in smooth muscle cells, which are the target of dihydropyridines, and thereby reduce muscle tone [194].

Moreover, the magnesium ion appears to suppress plasma aldosterone concentrations in humans [195]. Magnesium may also inhibit norepinephrine release from peripheral sympathetic nerve endings in spontaneously hypertensive rats by blocking calcium influx through N-type calcium channels [196]. Magnesium may exert its BP-lowering effects by decreasing intracellular sodium and cytoplasmic free calcium [197]. The combined intake of magnesium and taurine may lower SBP and DBP, possibly because both chemicals decrease intracellular calcium and sodium [197,198]. Therefore magnesium may potentially reduce BP by both direct and indirect actions on vascular smooth muscle cells.

Whether magnesium supplements per se lower BP in hypertensive individuals is controversial. Some studies show that magnesium reduces BP [199], whereas other studies do not [200]. The antihypertensive effects of magnesium supplementation are small in many of the studies that suggest such an effect. In one metaanalysis of 20 randomized clinical trials of magnesium supplementation in hypertensive persons (14 trials) and normotensive individuals (6 trials), 1220 persons were evaluated [199]. The dose of magnesium supplements ranged from 10 to 40 mmol/d with a median intake of 15.4 mmol/d. The pooled net estimates of BP changes with magnesium supplements showed only a small and statistically nonsignificant reduction in SBP, −0.6 mmHg (95% CI, −2.2 to +1.0), and DBP, −0.8 mmHg (95% CI, −2.1 to +0.5). There was no significant fall in SBP ($P = .06$) or DBP ($P = .17$) when the analysis was restricted to the 14 hypertensive trials. Nonetheless, this metaanalysis indicated a dose-dependent effect of magnesium on BP with an average reduction in SBP of −4.3 mmHg (95% CI, −6.3 to −2.2, $P < .001$) and in DBP of −2.3 mmHg (95% CI, −4.9−0.0, $P < .09$) for each 10 mmol/day (i.e., ~243 mg/day) increase in magnesium intake [199].

A more recent metaanalysis, including 34 randomized controlled trials and 2028 participants, but excluding people with active liver or kidney disease, demonstrated that magnesium supplements were associated with a significant reduction in SBP (weighted mean decrease, −2.00 mmHg; 95% CI, −3.58 to −0.43) and DBP (weighted mean fall, −1.77 mmHg, 95% CI, −2.82 to −0.73) [201]. The size of the dose and the duration of the magnesium supplements were related to the magnitude of reduction in BP. A higher dose (>300-mg Mg/day) and longer duration of treatment (>60 days) with the magnesium supplements increased serum magnesium levels and decreased BP significantly. Changes in serum magnesium were associated with a more robust reduction in DBP than in SBP, and only the reduction in DBP was statistically significant: −2.26 mmHg/0.1 mmol/L increment in serum magnesium (95% CI, −4.26 to −0.27) [201].

Larger intakes of magnesium, that is, 500−1000 mg/day, may be more likely to lower BP [202]. A metaanalysis of nine cohort studies, including 180,566 participants with 20,119 hypertensive patients, found an inverse association between dietary magnesium intake and the risk of hypertension [relative risk (RR): 0.92; 95% CI, 0.86−0.98] comparing the groups with the highest intakes to the groups with lowest intakes. The same study demonstrated a 5% reduction in the risk of hypertension for each 100 mg/day increment in magnesium intake (RR: 0.95; 95% CI, 0.90−1.00). On the other hand, serum magnesium concentrations were only marginally and negatively associated with the risk of hypertension in this study (RR: 0.91; 95% CI, 0.80−1.02) [203].

Many people with hypertension have CKD with reduced ability to excrete magnesium, and caution must be exercised in these individuals, because these persons may be at increased risk for hypermagnesemia if they ingest large magnesium supplements. It is suggested that a high magnesium intake may have a more pronounced BP-lowering effect when it is provided with a high potassium and low sodium intake [202].

Protein and amino acids

Epidemiological studies indicate an inverse relationship between protein intake and BP [204]. A small number of clinical trials indicate that supplements of soybean protein may decrease SBP or DBP [204−206]. A larger randomized, double-blind, controlled trial was carried out in 302 adults in China in which subjects were assigned to receive either 40 g/day of supplemental soybean protein or 40 g/day of complex carbohydrates [205]. All participants had prehypertension or stage 1 hypertension with an initial untreated SBP of 130−159 mmHg and/or DBP of 80−99. During the 12 weeks of treatment, SBP and DBP fell in both groups but decreased significantly more in the soybean protein−treated group. The greater decrease in BP in the soybean protein−treated participants over the complex carbohydrate-treated group was by −4.31 (95% CI, −6.51 to −2.11) mmHg systolic and −2.76 (95% CI, −4.16 to −1.35) mmHg diastolic at 12 weeks of intervention. In a subgroup analysis, there were significantly greater decreases in SBP (−7.88 mmHg) and DBP (−5.27 mmHg) in the soybean protein versus the carbohydrate-treated subjects who had stage 1 hypertension [205]. The prehypertensive individuals showed a trend, not significant, for a reduction in SBP and DBP. This study did not examine whether it was the protein or the isoflavones in the soybean that reduced the BP.

Another randomized crossover study investigated the effects on BP of increased protein intake [207]. The participants were allocated to three groups that each received a supplement. One group received 40 g/day of a supplement of soy protein; the second group received 40 g/day of milk protein. The third group received a supplement of 50 g/day of complex carbohydrates without protein. The patients displayed a statistically significant reduction in SBP only when they ingested either the soy protein or milk protein. The changes in SBP (mmHg) were −1.5 (95% CI, −2.4, −0.6), −1.8 (95% CI, −2.8, −1.0), and 0.5 (95% CI, −0.4, 1.3), respectively, with the soy protein, milk protein, and carbohydrate supplements (*P*-value for significance among the three groups: <0.001). Nonsignificant decreases in DBP were also demonstrated with both the soy protein and the milk protein groups (*P*-value between groups: 0.27) [207]. A metaanalysis, including 27 randomized controlled trials, was performed to investigate the effect of soya bean supplements on BP [208]. Many of these trials were of small size. The study demonstrated significant decreases in both SBP (weighted mean difference −2.21; 95% CI, −4.10, −0.33 mmHg, $P = .021$) and DBP (−1.44; 95% CI, −2.56, −0.31 mmHg, $P = .012$). The metaregression analysis of these trials indicated that the BP-lowering effects of the soya supplements were larger in the studies with higher mean pretreatment BPs [208].

Several potential mechanisms have been suggested to explain how soybean protein may reduce BP [205]. Soybean protein contains substantial amounts of arginine, which can be converted to nitric oxide, a potent vasodilator [209]. Intravenous injection of arginine reduces peripheral vascular resistance and decreases BP in humans [210]. Glutamic acid, which is high in vegetable proteins, may have special BP−lowering effects [211]. Digestion of proteins derived from foods may release bioactive peptides that inhibit the ACE and that probably have other antihypertensive actions [212]. Milk proteins are particularly likely to yield these peptides [212]. This might contribute to the antihypertensive effects of the DASH diet (see later). Protein may also increase urinary excretion of sodium, water, and free dopamine [213,214]. A dopamine-mediated natriuresis engendered by ingested protein may lower BP [214]. Soybean protein may increase insulin sensitivity and glucose tolerance [215]; since insulin resistance and consequent hyperinsulinemia may predispose to hypertension (see earlier), this latter effect of soybean protein may decrease BP [216]. Soybeans contain bioactive polyphenolic compounds or isoflavones. These compounds can reduce BP by increasing the production of nitric oxide, and also by modulating the activities of potassium or calcium channels [217].

An epidemiological study of 3588 Dutch adults followed for up to 10 years reported that greater ingestion of grain protein was associated with a small decrease in the incidence of hypertension; HR = 0.85; 95% CI, 0.73−1.00; $P_{\text{trend}} = .04$ for the risk of new-onset hypertension between the upper and lower tertiles of protein intake from grain [218]. The effect of protein intake on BP was confirmed by a metaanalysis of 40 randomized controlled trials with 3277 participants. The sources of protein were from animals (meat, fish, and dairy products), vegetables (including but not limited to soy), and mixed (animal and vegetable proteins combined) [219]. This study demonstrated that increased protein intake was associated with lower SBP (weighted mean difference, −1.76; 95% CI, −2.33, −1.20 mmHg) and DBP (−1.15 mmHg; 95% CI, −1.59, −0.71) compared an increase in carbohydrate or lipid intake. Plant protein and animal protein both lowered SBP and DBP significantly and to similar degrees [219]. Notwithstanding the modest BP-lowering effects of protein supplements, large protein intakes may not be indicated for many individuals who have diseases that render them protein intolerant, such as CKD, acute kidney injury, or liver failure.

Fiber

Dietary fiber is considered part of a healthy diet that may exert protective effects on the gastrointestinal tract and cardiovascular system. Streppel and coworkers carried out a metaanalysis showing that increasing dietary fiber intake in Western populations, where the usual fiber intake is well below recommended levels, may help to prevent hypertension [220]. In another metaanalysis, Whelton and coworkers reported that increased intake of dietary fiber may reduce BP in hypertensive patients; in normotensive individuals, there was no reduction in BP [216]. A recent extensive metaanalysis of both observational and interventional studies, involving 135 million person-years, investigated the effect of fiber intake on health-related outcomes, including changes in body weight, hemoglobin A1c (HbA1c), serum total cholesterol, and BP. This study also demonstrated that higher dietary fiber intake was significantly associated with decreased SBP (mean difference, −1.27 mmHg; 95% CI, −2.50, −0.04) [221].

A randomized controlled trial in hypertensive individuals indicated that dietary protein and fiber has significant, additive effects on lowering both 24-hour and awake SBP [206]. It is possible that some of the antihypertensive effects of dietary sodium restriction may involve changes in the intake of other nutrients such as fiber. Sciarrone and associates report that reduction in sodium intake may decrease the dietary content of both fats and fiber, which might independently affect BP and lipid metabolism [222]. In a more recent, rather small-scale study lasting 12 weeks, overweight and obese adults were randomly assigned to ingest their usual diet with placebo (the control group), their usual diet with 21 g/day of a psyllium fiber supplement, or a healthy diet with placebo [223]. The fiber intake of the participants assigned to the healthy diet, which did not include a fiber supplement, was evaluated at weeks 6 and 12. At these two times the actual fiber intake with the healthy diet exceeded the fiber intake in the usual control diet (without the fiber supplement) by 11.9 and 11.0 g/day, respectively. However, this increase in fiber intake with the healthy diet at weeks 6 and 12 was not as great as with the psyllium fiber supplement, which was 18.4 and 20.6 g/day at these two times [223]. In the subjects who completed the 12-week study, those who were fed the psyllium supplement, in comparison to the people fed the control diet, manifested a lower SBP and DBP only at 6 weeks ($P = .04$ and .04, respectively), whereas the group fed the healthy diet with increased fiber showed a lower SBP only at 12 weeks and a lower DBP only at 6 weeks ($P = .02$ and .04, respectively). Hence, this latter study did not provide evidence of an important BP-lowering effect of psyllium fiber.

Alcohol

Excessive alcohol intake often increases BP. However, these effects are generally transient, and BP usually falls rapidly when individuals stop drinking alcohol [224]. A time-dependent association between alcohol consumption and BP levels was reported by Moreira in experimental studies of free-living individuals. In contrast, in another study the frequency of alcohol consumption and type of beverage ingested were not found to be independently associated with BP levels [225].

African-American subjects who consumed large amounts of alcohol showed a high risk of developing hypertension [226]. Consumption of low-to-moderate amounts appears to be associated with a higher risk of hypertension in black men but not in white men or black or white women [227]. Also, in Chinese males, a higher intake of alcohol is associated with a higher risk for isolated systolic hypertension, both systolic and diastolic hypertension, and isolated diastolic hypertension [228]. In the North American free-living population, the consumption of alcohol in amounts >210 g/week is reported to be an independent risk factor for hypertension [227]. In hypertensive individuals, heavy alcohol consumption leads to a significant increase in the risk of cerebral hemorrhage, suggesting a synergistic effect of alcohol and hypertension [229]. On the other hand, light alcohol consumption significantly reduces the risk of ischemic stroke [230].

Metaanalyses indicate that a gender difference exists between the association of the amount of alcohol consumed and the prevalence of hypertension [231,232]. In men, there was a linear, dose-dependent relationship between alcohol consumed and hypertension. In women a modest alcohol intake (less than 10 g/day) was associated with an attenuation in the prevalence of hypertension, though alcohol intake of 30 g/day or more was significantly associated with a higher prevalence of hypertension [232]. Hence, a *J*-curve association between alcohol intake and the risk of hypertension was observed in women, whereas a linear association was observed in men [231,232]. The mechanism for this gender difference is unclear [231,232]. Of interest a Japanese cohort study conducted for 10 years that involved 123,764 participants found that ethanol intake of <20 g/day was associated with a lower incidence of hypertension or new onset of stage 3 or more severe CKD [233]. This association was significant in men (HR 0.86; 95% CI, 0.78−0.95) but marginal in women (HR 0.80; 95% CI, 0.63−1.02) [233].

The mechanisms involved in alcohol-generated hypertension appear to include the upregulation of the central or peripheral SNS, activation of the renin−angiotensin system, attenuation of baroreceptor activity, increase in calcium within vascular smooth muscle cells, and endothelium dysfunction characterized by a decrease in NO production and an increase in endothelin production [234,235]. Zilkens and coworkers studied 24 healthy men who underwent four interventions, in random order, for 4 weeks each [236]: (1) abstinence from all alcohol and grape products; (2) an intake of 375 mL per day of red wine containing 39-g alcohol; (3) an intake of 375 mL per day of dealcoholized red wine; or (4) an intake of 1125 mL per day of beer providing 41-g alcohol. Daily consumption of about 40 g of alcohol either as red wine or beer resulted in a similar mild increase in 24-hour SBP and awake SBP and 24-hour heart rate, whereas dealcoholized red wine did not lower BP. The red wine, beer, and dealcoholized red wine did not affect vascular function (i.e., flow-mediated vasodilation). These observations suggest that in men it is the alcohol in red wine and beer that increases SBP, and that nonalcoholic components of red wine do not mitigate the BP-elevating effects of alcohol [236]. One metaanalysis indicated that the reduction of alcohol consumption in those who regularly take three or more drinks per day resulted in a significant decrease in both SBP and DBP. These findings reinforce the thesis that large intakes of alcohol increase BP [237]. Notwithstanding evidence that alcohol, particularly in larger amounts, is associated with increased BP, there are abundant epidemiological data indicating that alcoholic drinks, and possibly particularly red wine, may reduce the risk of death from cardiovascular disease. The mechanisms for this protective effect are not completely understood and may involve the actions of alcohol per se and possibly also the effects of the antioxidant and vasodilator phenolic compounds.

Vitamin D

Vitamin D deficiency (deficiency of 25-hydroxy cholecalciferol [25(OH)D]) is reported to occur commonly throughout the world, especially in Asia, the Middle East, and Africa [238–240]. In low- and lower middle-income countries, almost 50% of the population is reported to exhibit serum 25(OH)D below 25 nmol/L [240]. Vitamin D *insufficiency* is often defined as a serum 25(OH)D concentration of 20–30 ng/mL (50–75 nmol/L), and vitamin D *deficiency* is defined as 25(OH)D level below 20 ng/mL ($<$50 nmol/L) [238]. Approximately 80%–90% of the body's vitamin D levels are considered to come from the effects of sunlight on the skin [238], and the high risk of vitamin D deficiency is considered to be due to reduced outdoor activities, efforts to avoid sun exposure, air pollutants, living at high latitudes, dark skin, frequent use of sunscreens, protective clothing against the sun, and the impaired ability of older people to produce vitamin D in the skin in response to sunlight.

Knockout mice for the vitamin D receptor or the 1α-hydroxylase enzyme develop high renin hypertension and cardiac hypertrophy [241,242]. In hypertensive patients, there may be an inverse relationship between PRA and serum 1,25$(OH)_2$D levels [243]. Studies at the cellular and molecular levels indicate that 1,25$(OH)_2$D is a negative regulator of renin gene expression due to the binding of the vitamin D receptor to the transcription factor cyclic adenosine monophosphate-response element-binding protein [244].

1,25$(OH)_2$D also suppresses vascular endothelial and smooth muscle cell tissue factor, thrombospondin, and plasminogen activator inhibitor-1 and increases the synthesis of vascular endothelial growth factor, prostaglandin, and hepatic thrombomodulin [245]. These effects would appear to be cardioprotective, inhibitory of thrombosis, and promotive of fibrinolysis [245,246].

Epidemiological and other studies also suggest that, in addition to bone mineral and divalent ion metabolism, vitamin D may also reduce insulin resistance and have vascular protective, renoprotective, and antiinflammatory effects [247–250]. Hence, vitamin D may not only reduce BP but may also prevent or ameliorate a number of vascular and renal complications of hypertension. On the other hand, excessive vitamin D intake with toxicity [e.g., serum 25(OH)D $>$150 ng/mL ($>$374.4 nmol/L)] may induce hypercalcemia, arterial stiffness, hypertension, and progressive renal failure [238].

Some, but not all cross-sectional epidemiological studies describe an inverse relation between serum 1,25$(OH)_2$D and especially 25(OH)D levels and SBP or DBP [245,246]. Clinical trials of vitamin D supplementation on BP also are not consistent. One double-blind trial of 1200-mg calcium/day alone or with cholecalciferol of 800 IU/day in elderly vitamin D deficient women showed significant reductions in SBP and DBP in both groups, but with a significantly greater reduction in SBP in the vitamin D–treated group ($P = .02$) [251]. Most, but not all, of the other trials of vitamin D supplements on SBP or DBP were negative [246]. A metaanalysis, including 17 randomized control trials and 1687 participants, reported that oral vitamin D_3 did not have a significant effect on BP in vitamin D–deficient people, although oral vitamin D_3 was associated with a reduction in SBP in people who were both vitamin D deficient and either more than 50 years old, obese (BMI ≥ 30 kg/m^2) or hypertensive [252].

It has been argued that most of these studies were not primarily or adequately designed to assess the effects of vitamin D on BP; the subjects were not hypertensive or vitamin D deficient; the vitamin D dose might have been too low (e.g., 400 IU/day) or the BPs may not have been measured in a sophisticated fashion [246]. An example is the Women's Health Initiative (WHI) which conducted the largest randomized clinical trial of vitamin D [253]. This trial, which was carried out for a mean of 7 years, randomized over 32,000 postmenopausal women to receive 400 IU vitamin D plus 1000-mg calcium/day or placebo. Although there were no significant differences in changes in SBP or DBP or in the incidence of hypertension during the study, it is possible that the vitamin D dose was too small.

A randomized controlled trial investigated the effects of providing cholecalciferol, 50,000 IU/week, for 8 weeks to patients with essential hypertension and reduced plasma vitamin D levels [25(OH)D $<$ 30 ng/mL]. In the patients receiving the vitamin D supplements, PRA decreased from 1.51 ± 0.4 to 1.17 ± 0.3 ng/mL/hour, $P = .02$, and plasma angiotensin II fell from 15.8 ± 2.7 to 11.6 ± 1.6 pg/mL, $P = .02$. However, endothelial function, measured by flow-mediated dilatation of the radial artery, did not improve in the treatment group. BP also did not decrease after the administration of vitamin D in the hypovitaminosis D patients [254]. In another double-blind, randomized controlled trial of overweight patients with vitamin D deficiency, ergocalciferol 50,000 IU/week did not reduce renin–angiotensin system activity or BP [255]. However, these patients did not have hypertension.

Supplementation with 1,25$(OH)_2$D or its analogs, paricalcitol or 1α-hydroxyvitamin D, has also given inconsistent results with regard to BP reduction [246]. The PRIMO Trial studied 115 patients with stage 3 or 4 CKD, left ventricular hypertrophy, and preserved left ventricular ejection fraction who were randomized to receive paricalcitol, 2.0 μg/day, and 112 similar patients randomized to placebo for up to 48 weeks [256]. The paricalcitol dose could be reduced to 1 μg/day if patients became hypercalcemic. Of patients, 96% were hypertensive. SBP or DBP did not differ significantly during the course of the study. More well designed, adequately powered randomized controlled clinical trials are needed to definitively assess the possible effects of vitamin D on BP.

Ultraviolet radiation increases the endogenous vitamin D. Exposure to ultraviolet B radiation for 12 weeks did not change BP compared to ultraviolet A radiation, although the mean 25(OH)D levels increased in the group irradiated by ultraviolet B [257]. On the other hand, an epidemiological study of 1410 Chinese residents in Macau revealed that the amount of habitual sunlight exposure each day was negatively associated with the presence of hypertension, and that sun exposure for more than half an hour per day was associated less with hypertension (OR 0.6, 95% CI, 0.4−0.8) [258].

Chocolate

A randomized, crossover, short-term (7-day) study was conducted to assess the effect of chocolate ingestion on BP in 20 patients with grade I essential hypertension who had never received antihypertensive treatment [259]. Eating dark chocolate, but not white chocolate, was associated with a significant lowering of SBP (−11.9 ± SD 9.7 mmHg, $P < .0001$) and DBP (−8.1 ± 5.0 mmHg, $P < .0001$). The authors suggest that dark chocolate may lower BP by its high content of flavonols that induce vasorelaxation. Dark chocolate has also been shown to decrease isolated systolic hypertension in geriatric patients [260] and, in one [261] but not in all studies [262], in healthy persons. Hypertensive patients who took a combination of antihypertensive medicines and flavonoids from dark chocolate, dried red apples, and green tea displayed a greater decrease in both SBP and DBP as compared to those who took antihypertensive drugs alone [263].

The possible antihypertensive effects of chocolate or its cocoa product were investigated by several metaanalyses [264−266]. These studies demonstrated that both SBP and DBP decreased after intake of chocolate or cocoa products. One metaanalysis provided evidence that cocoa or chocolate intake was associated with a reduction in SBP and DBP of −1.76 (95% CI, −3.09, −0.43) mmHg, and −1.76 (95% CI, −2.57, −0.94) mmHg, respectively. These BP-lowering effects of chocolate or cocoa were more evident among the patients with higher baseline BP measurements [266]. Another study indicated that the intake of flavonol-rich chocolate or dark chocolate, in contrast to white chocolate or low-flavonol chocolate, was associated with improvement in the insulin resistance index and fasting insulin levels [265].

Coffee and caffeine

Suzuki et al. showed hypotensive effects of green coffee bean extract and its metabolites in spontaneously hypertensive rats [267]. Kozuma et al. reported a dose−responsive antihypertensive effect of green coffee bean extract given to mildly hypertensive individuals for 28 days [268]. These findings were confirmed by Watanabe and coworkers who studied essential hypertension in rats and humans [269]. The BP-lowering effect of green coffee bean extract is attributed to the effects of chlorogenic acid, a biologically active dietary polyphenol, and its metabolites on vascular reactivity [267−270].

Interestingly, the roasted-coffee extract may not have these antihypertensive effects [267], possibly because chlorogenic acid is easily degraded by heat. Caffeine induces fluctuations in BP by stimulating not well-specified cardiovascular mechanisms [271]. Corti studied the acute effects of coffee in volunteers who drank a triple espresso or a decaffeinated triple Espresso or who were infused intravenously with 250 mg of caffeine. The subjects, who were nonhabitual coffee drinkers, showed an increase in sympathetic nerve activity, measured by microneurography in muscle, and a rise in BP after receiving the coffee which was independent of whether caffeine was present [272]. A clinical trial demonstrated that two cups of coffee (600 mL total) were associated with an elevation in BP and mitigation of the BP-lowering effects of the calcium channel blocker felodipine on both brachial and aortic BP that lasted for up to 8 hours [273]. The mean differences in brachial artery SBP and DBP with coffee plus felodipine versus felodipine without coffee were 3.8 (95% CI, 1.1, 6.4) and 1.5 (95% CI, 0.2, 2.8) mmHg, respectively, during the 5−8 hours after coffee ingestion. These results indicate the amount of coffee ingested and the time after its consumption that might be taken into consideration when assessing its possible effects on BP measurements in hypertensive patients [273].

An acute effect of caffeine on BP in hypertensive patients was confirmed by a metaanalysis, which demonstrated that SBP increased by 8.14 mmHg (95% CI 5.68, 10.61) for up to 180 minutes after ingestion of 200−300 mg of caffeine [274]. Consumption of either sugar-containing or diet cola beverages has also been associated with increased risk for hypertension, possibly due to its caffeine content [275]. Thus the foregoing studies suggest that both coffee with or without caffeine and caffeine alone can each independently increase BP.

On the other hand, the chronic effects of coffee consumption on BP are somewhat different from the acute effects described earlier and are often conflicting. A metaanalysis of 11 interventional trials of coffee drinking, 10 of which were randomized and controlled, which encompassed the controlled studies published between 1983 and 1994, demonstrated that coffee consumption increased SBP and DBP by 2.4 (range, 1.0–3.7) and 1.2 (range, 0.4–2.1) mmHg, respectively [276]. The population of the studies included in this metaanalysis was relatively young (median age, 38 years old), was studied for a short duration of time (median duration, 56 days), and was normotensive at baseline (median values of average BP, 119/71 mmHg). However, another metaanalysis, including both randomized controlled trials and cohort studies, indicated that coffee consumption did not significantly affect either BP or the incidence of hypertension [277]. A number of the studies in this metaanalysis were considered to have low-quality evidence. Moreover, two other dose–response metaanalyses of cohort studies of coffee intake indicated that consumption of many cups of coffee, that is, more than six cups per day, was associated with a lower incidence of hypertension [278,279]. The risks of incident hypertension were 0.99 (95% CI, 0.98–1.00) [278] and 0.98 (95% CI, 0.98–0.99) [279], respectively, in these two studies.

Pregnancy

The effect of coffee or tea intake on BP in pregnant women is controversial. A cohort study of 7890 pregnant women [280] found that high coffee or tea intake was associated with higher SBP in the first and third trimesters (*P* for trend .014 and .009, respectively) but not in the second trimester (*P* for trend .441), whereas higher coffee or tea intake was not associated with DBP in any trimester. The authors ascribe these effects on SBP to the high caffeine content in these drinks [90 mg of caffeine (equal to 1 unit) in a 125-mL cup of regular coffee and 45 mg of caffeine (equal to 0.5 unit) in a regular cup of tea.]. The analyses appear to be adjusted for the intake of decaffeinated coffee and tea. Interestingly, women imbibing a caffeine intake from coffee of 180 to about 350-mg caffeine/day from coffee or tea appeared to have a lower incidence of preeclampsia than women drinking <180-mg caffeine/day from coffee or tea (OR: 0.63, 95% CI 0.40, 0.96) [280].

A case-crossover design study that involved 286 pregnant women with preeclampsia found that the frequency of caffeine exposure from coffee, tea, and colas was inversely associated with the risk of preeclampsia [281]. The patients completed a questionnaire regarding their medical history, current health, and recent activities. The frequency at which coffee, tea or colas, spicy food, and alcohol were consumed during the 7 days before presenting with preeclampsia, as compared to the week before, was each associated with a lower incidence of preeclampsia (for caffeine, OR 0.51, 95% CI 0.33, 0.77) [281]. Another prospective multicenter case–control study in Ethiopia had different findings. This study investigated factors, including coffee intake, that were associated with the incidence of preeclampsia [282]. The cases studied were pregnant women diagnosed with preeclampsia or eclampsia either during a prenatal clinic visit or when they presented to the facility in labor. Controls were normotensive women delivered in the same facilities at the same time as the patients with preeclampsia or eclampsia. After adjustment for covariates, daily coffee intake was associated with higher incidence of preeclampsia or eclampsia (OR 1.78, 95% CI 1.20, 3.05) [282].

Tea

The relationship between BP and tea drinking is particularly relevant, because the volume of tea consumption is second only to water intake in the world [283]. The effect of tea on BP may be less consistent than the effects of coffee according to different reports [284]. However, Yang and coworkers report that chronic consumers of moderate amounts of green or oolong tea are less likely to develop hypertension [285]. This effect may be due to flavonoids, which affect endothelial function [286]. Green, oolong, and black tea contain a number of flavonoids and other compounds that, in animal and human studies, engender vasodilatation, protect against endothelial dysfunction, and have antioxidant, antiinflammatory, or hypolipidemic effects [283,287,288]. Grassi et al. investigated the effect of 150 mg of tea flavonoids twice daily for 8 days on endothelial function and circulating angiogenic cells. They found that ingestion of tea flavonoids increased flow-mediated dilatation and endothelial progenitor cells [289]. However, in another double-blind study, normal subjects were studied twice, once after they drank three cups of black tea which contain about 400 mg of flavonoids and once after drinking a similar-appearing placebo [290]. The black tea did not appear to affect endothelial function, since the resistance to forearm arterial blood flow in response to several vasodilators was not different when the subjects drank black tea as compared to placebo.

Hodgson et al. showed that consumption of foods altered the acute beneficial effects of tea on BP in humans [291]. A meal ingested with tea blunted the

BP-lowering effect of tea; the decrease in SBP with tea was smaller when it was ingested with meals, whereas flow-mediated dilatation was not changed by tea intake with or without meals.

A controlled trial was conducted in 95 regular tea drinkers who were randomized to drink three cups/day of black tea or placebo for 6 months [292]. Mean 24-hour baseline SBP and DBP were 121.4 and 72.9 mmHg, respectively. Compared with placebo, at 6 months, the black tea drinkers sustained a significant decrease in 24-hour ambulatory SBP (−2.0 mmHg, $P = .05$) and DBP (−2.1 mmHg, $P = .003$). The 24-hour ambulatory SBP and DBP were also significantly lower in the black tea–-drinking participants at 3 months [292]. Similarly, another trial investigated the BP-lowering effect of green tea extract in obese prehypertensive women. This study showed that green tea extract intake for 4 weeks significantly reduced 24-hour, daytime, and nighttime BP measured by ambulatory BP monitoring [293]. Several metaanalyses have investigated the effects of tea drinking on BP. A metaanalysis on green tea drinking demonstrated reductions of SBP and DBP by −2.05 (95% CI, −3.06, −1.05) and −1.71 (95% CI, −2.86, −0.56) mmHg, respectively [294]. A metaanalysis on black tea drinking also revealed decreases in both SBP and DBP by −1.8 (95% CI, −2.8, −0.7) and −1.3 (95% CI, −1.8, −0.8), respectively [295]. Sour tea (*Hibiscus sabdariffa* L.) is also known to reduce BP. A metaanalysis demonstrated that sour tea was associated with a decrease in both SBP (by −7.58 mmHg; 95% CI, −9.69, −5.46) and DBP (by −3.53 mmHg; 95% CI, −5.16, −1.86), although there was large heterogeneity in the results [296]. Taken together, these studies suggest that tea intake may acutely decrease BP and may or may not affect endothelial function. Consuming tea with food may attenuate the BP-lowering effect but chronic intake of green, black or oolong tea is likely to decrease BP.

Urate

As indicated in the previous discussion on obesity, elevated serum urate levels may predispose to hypertension. Metaanalyses that examined the association of hyperuricemia with incident hypertension [297] and prehypertension [298] showed that patients with hyperuricemia are more likely to develop prehypertension or hypertension. The risk ratio for hypertension in patients with hyperuricemia was 1.48 (95% CI, 1.33, 1.63) and 1.15 (95% CI, 1.06, 1.26) for each 1 mg/dL increase in serum uric acid levels [297].

In a double-blind, placebo-controlled, crossover trial in adolescents with newly diagnosed stage 1 essential hypertension and with serum urate levels of 6.0 mg/dL or greater, short-term treatment with allopurinol, which decreased serum urate levels, lowered BP [296]. Of the 30 participants in this study, 22 were overweight or obese. A metaanalysis of the effect of allopurinol on BP reduction in hyperuricemic patients who did or did not have hypertension demonstrated a small but significant decrease in both SBP, −0.321 mmHg (95% CI, −0.497, −0.145, $P < .001$), and DBP, −0.260 mmHg (95% CI. −0.102, −0.417, $P = .001$) [299]. Fructose intake predisposes to urate formation, and as indicated earlier, fructose intake is directly correlated with SBP and DBP in people with higher urinary sodium excretion [54].

Dietary, surgical, and lifestyle strategies to prevent or treat hypertension

In addition to increasing or reducing the intake of nutrients that may affect BP, which are reviewed earlier, specific preventive and therapeutic nutrition-related strategies have been developed to prevent or treat hypertension. These strategies involve dietary management, surgical procedures, and lifestyle changes, and they will be discussed in the following sections. Methods for the prevention of excessive fat gain and weight reduction treatments utilizing healthy lifestyles and reduced energy intake or bariatric surgery are discussed in Chapters 40–42. The following comments briefly summarize these approaches, particularly with regard to the prevention or treatment of hypertension.

Bariatric surgery

Weight reduction by dietary intervention or bariatric surgery in obese, hypertensive persons, with or without diabetes mellitus or CKD, is now widely performed and is generally associated with a decrease in BP [300]. Programs have been designed to lower dietary energy intakes, fat mass, and BP and generally include a more global health-oriented approach that also emphasizes an overall healthier diet and lifestyle. These programs will be discussed later. The effects of medicine-induced weight loss on hypertension will also briefly discussed [57,301–303].

The clinical experience with bariatric surgery is discussed in detail in Chapter 41, Bariatric Surgery and Kidney Disease. In general, weight loss is substantially greater with bariatric surgery than with diet and lifestyle treatments (see later), particularly when the effectiveness of treatment is evaluated over periods of time measured in years rather than just a few months. Some types of bariatric surgery appear to be the most reliable and effective methods available for reducing fat mass in obese individuals, including patients with diabetes mellitus [66,300,304–306]. Reversal of type 2 diabetes in obese individuals appears to be much more common with bariatric surgery than with diet and lifestyle changes alone [66,306] (Chapters 40–42). A metaanalysis of six randomized controlled studies indicated that bariatric surgery was strikingly more effective than the combination of medical treatment and attempted dietary interventions and lifestyle modifications for attaining a long-lasting remission of type 2 diabetes; the OR was 76.4 (95% CI, 20.7, 281.7) [307]. The same metaanalysis demonstrated that SBP was significantly lower in the bariatric surgery group than the medical treatment, dietary intervention, and lifestyle changes group (mean difference −2.83 mmHg, 95% CI −4.88, −0.78, $P < .01$), while DBP was not (mean difference 0.28 mmHg, 95% CI −1.89, 2.45 mmHg, $P = .80$) [307].

It should be emphasized that successful bariatric surgery programs also include counseling to reduce energy intake and to adopt a healthier lifestyle as well as the surgical procedure itself. After surgery the types and volumes of foods that can be ingested by the patient may need to be dramatically changed. Of the several types of bariatric surgery most commonly used, gastric banding and sleeve gastrectomy are less invasive than some of the other procedures employed, and the incidence of serious complications tends to be lower. But weight loss may be greater and more sustained with the more extensive types of surgery (see Chapter 41: Bariatric Surgery and Kidney Disease [66]). Overall, the complication rates with bariatric surgery are not high. Accumulating evidence suggests that the procedure has long-lasting effectiveness in both diabetic patients [308,309] and hypertensive patients [309]. Evidence from long-term follow-up suggests that weight loss, reduced glycemia, and cardiovascular risk may be sustained for 10 or more years after bariatric surgery [300,304,308]. Bariatric surgery is becoming an increasingly common option to attain long-term weight reduction for people who are refractory to weight reduction by dietary and lifestyle changes alone (please see Chapters 40–42).

Health-enhancing diets and lifestyles

For over 30 years, there has been a growing focus on the use of complex, health-enhancing diets to prevent or treat hypertension, usually of the mild-to-moderately severe variety. The composition of these diets is generally based on evidence that the individual constituents of these diets have preventative or therapeutic effects on hypertension. Much of this evidence is summarized in the first part of this chapter. Experience regarding the effectiveness and patient adherence to these diets is discussed next.

The hypertension prevention trial

The Hypertension Prevention Trial (HPT) was a multicenter trial in which 841 adults with DBPs of 78–89 mmHg were randomly assigned to one of four dietary counseling treatments (decreased energy intake, decreased sodium intake, decreased sodium and energy intake, or decreased sodium and increased potassium intake) or to a control group that did not receive dietary counseling [310]. Men and women with lower BMIs ($n = 211$) were not assigned to the two low energy–intake groups. Subjects assigned to one of the four treatments underwent group counseling weekly for the first 10 weeks, then every other week for the next 4 weeks, and finally bimonthly for the duration of the study. Phone calls, newsletters, and other methods were employed to facilitate training and compliance. People were followed for 3 years. Attendance at scheduled counseling sessions declined significantly with time. At 6 months, overnight urine sodium excretion had fallen by 13%, urine potassium increased by 8%, and body weight fell by −7% as compared to changes in the control group. At 3 years the reductions in urine sodium and body weight, compared to changes in controls, were −10% and −4%, respectively, whereas there was no change in urine potassium. The net reductions in weight in the low energy groups at 3 years were due, in large part, to the increase in weight in the control group. BP decreased from baseline in all treatment groups, including the controls. The largest net reduction in SBP and DBP occurred in the low energy group alone, −5.1 and −2.4 mmHg and −2.8 and −1.8 mmHg, at 6 months and 3 years, respectively ($P < .05$ for each BP at each time). The sodium reduction groups sustained a significantly lower composite rate of hypertensive events (i.e., SBP $\geq$ 140 mmHg, DBP $\geq$ 90 mmHg or intake of antihypertensive medicines); the other treatment groups experienced a nonsignificant trend in this same direction.

The trials of hypertension prevention: TOHP Phase I

The trials of hypertension prevention (TOHP) was a multicenter trial involving two phases. TOHP Phase I was a short-term trial designed to test the effect of three different lifestyle interventions and four nutritional supplements on BP control in individuals with high-normal DBP. TOHP Phase II was designed to test more long term, for 36–48 months, those interventions that were demonstrated in TOHP Phase I to lower BP. In Phase I, 2182 men and women with average high-normal DBP (80–89 mmHg) and with SBP $\leq$ 160 mmHg were randomized in a parallel-controlled fashion to receive either lifestyle modification or nutritional supplementation. The interventions undertaken in the life-style modification component of the study included weight loss intervention, dietary sodium reduction, stress management, or usual care (UC). In the parallel nutritional supplement component of the study, nutritional supplements in the form of calcium or magnesium in stage 1 and fish oil or potassium in stage 2, as well as placebo, were given to the participants for 18 months [311,312]. The four nutritional supplements and the placebo were fed in a double-blind design. The nutritional supplements were fed in two stages, each of 6-month duration. In stage 1, participants were fed a supplement providing, each day, 1.0-g calcium, 360-mg magnesium or placebo. After a washout period, they entered stage 2, where they were rerandomized to be fed a supplement providing, each day, 6-g fish oil (containing 3.0-g omega-3 fatty acids), 60-mmol potassium or placebo. The weight loss, sodium reduction, and stress management groups underwent weekly group counseling sessions for 14, 10, and 8 weeks, respectively, and then at semimonthly or monthly intervals for the rest of the 18-month intervention.

In TOHP Phase I, in a comparison of baseline data to the final measurements, the weight reduction intervention produced a weight loss of −3.9 kg ($P < .01$) and a decrease in SBP of −2.9 mmHg ($P < .01$) and DBP of −2.3 mmHg ($P < .01$) [312]; the sodium reduction diet decreased urine sodium excretion by −44 mmol ($P < .01$), SBP by −1.7 mmHg ($P < .01$), and DBP by −2.9 mmHg ($P < .05$). There was no significant decrease in SBP or DBP between the baseline and final measurements with either stress management or the UC despite evidence for good compliance. Essentially similar results were observed for the lifestyle interventions at the 6-month follow-up, or for the nutritional supplements at the 3-month follow-up, except that DBP fell significantly at 3 months with the potassium supplement [312]. A posttrial follow-up evaluation 7 years later of 181 of the subjects indicated that the weight loss group and dietary sodium restriction group displayed a 77% and 35% decrease, respectively, in the OR of having hypertension [311].

The trials of hypertension prevention: TOHP Phase II

TOHP Phase II tested whether weight loss, reduced sodium intake, or a combination of weight loss and reduced sodium intake will decrease DBP, SBP, or the incidence of hypertension (defined as DBP of 90 mmHg or greater, SBP 140 mmHg or greater, and/or the use of antihypertensive medications) in overweight or moderately obese individuals with high-normal DBP (83−89 mmHg) and SBP below 140 mmHg at entry into the study [313−316]. A total of 2382 men and women who were 110%−165% above desirable body weight were randomly assigned to these three treatment arms or to a UC group in a two by two factorial design where they were assigned to weight loss or no weight loss and to sodium reduction or no sodium reduction. Subjects were followed for 3−4 years. Patients participated in group meetings and received individual counseling during this time, which initially was intensive and then became less frequent as the study progressed. Body weight, urinary sodium, and BP were measured every 6 months, and at 18 and 36 months, BP was measured over a series of three visits separated from each other by 7−10 days.

The participants who received the combination of weight loss and sodium reduction (the combined group) exhibited mean body weight loss of −4.1, −2.2, and −0.3 kg at 6, 18, and 36 months, respectively [314,315]. The UC group displayed a progressive weight gain that reached +1.8 kg at 36 months. The decrease in weight in the weight loss groups, calculated as the difference between the weight change in the two weight loss groups combined and the weight change in the UC group, was significantly negative at each of these three time points. Mean SBP and DBP decreased by −6.2/−5.6, −3.9/−4.5, and −0.5/−3.0 mmHg, respectively, in the combined group at 6, 18, and 36 months. The reductions in SBP and DBP were each significantly greater in the two weight loss groups combined as compared to the UC group at these three time points.

Urinary sodium excretion decreased, on average, by −64.3, −45.4, and −34.1 mmol/day in the combined group at 6, 18, and 36 months, respectively. In the UC group, urinary sodium decreased by −27.6, −16.8, and −10.5 mmol/day at these three time points [314]. The fall in urinary sodium excretion in the two sodium reduction groups, calculated as the difference between the decrease in urinary sodium in the two sodium reduction groups combined, and the decrease in urinary sodium in the UC group, was significantly greater at 6, 18, and 36 months. The decrease in mean SBP and DBP in the combined group was −5.1/−4.4, −3.8/−4.4, and −0.7/−3.0 mmHg, respectively, at these three time points. In the two sodium reduction groups combined, as compared to the UC group, the reduction in SBP was significantly greater at all three time points, whereas the reduction in DBP was significantly greater only at 6 and 18 months.

Throughout the 48 months of the TOHP Phase II clinical trial, the incidence of hypertension, defined as SBP ≥ 140 mmHg or DBP ≥ 90 mmHg or the use of antihypertensive medicines, was less, and usually statistically significantly less, in the two weight loss groups combined, in the two sodium reduction groups combined and in the weight loss and sodium reduction intervention group as compared to the UC group (average relative risks, 0.78−0.82). Those subjects who displayed greater and sustained weight loss had the greatest reduction in BP and the lowest risk ratio for hypertension. The effects of weight loss and decreased sodium chloride intake combined were not additive. After 6 months of treatment, the two interventions were less effective in maintaining both weight loss and low sodium intake, and, possibly for these reasons, the reduction in BP was also attenuated [314–316]. The results of the HPT, TOHP Phase I, and TOHP Phase II trials demonstrate that in overweight or moderately obese individuals, dietary modifications that reduce body weight and dietary sodium intake will reduce BP, but that weight loss, reduced sodium intake, and the decreased BP are difficult to sustain for 2–3 years or longer.

The dietary approaches to stop hypertension diet

The DASH study provides much relevant information concerning appropriate dietary therapy to control BP [317]. The DASH study was a multicenter study that compared a "control" typical American diet (low in fruits, vegetables, dairy products, essential minerals, and fiber, and high in saturated and total fat) to a diet rich in fruits and vegetables and also to a combination diet rich in fruits, vegetables, and low-fat dairy products and with a reduced saturated and total fatty acid content. The study was conducted in 459 adults with a mean age of 44 years, SBPs <160 mmHg, and DBPs of 80–95 mmHg. About 65% of the study subjects were racial minorities, especially African-American.

The control diet was fed to all subjects for 3 weeks, and individuals were then randomly assigned to remain on this diet or to ingest the diet rich in fruits and vegetables or the combination diet for an additional 8 weeks. All meals were prepared for the participants in a research kitchen, and five meals per week were ingested on the study site. The study used food rather than nonfood sources of calcium. As can be seen from Table 37.4, the control "American" diet was low in calcium, potassium, and magnesium; the average daily intake of these three minerals was close to the 25th percentile of dietary consumption by the US population, whereas the daily intake of calcium, potassium, and magnesium in the other two diets was close to the 75th percentile in the United States. The sodium content of all diets was similar. Baseline SBPs and DBPs averaged 131.3 ± SD 10.8 and 84.7 ± 4.7 mmHg, respectively. Hence, many individuals had only high-normal or normal BPs.

After the subjects commenced their experimental diets, there was a rapid, significant, and sustained fall in SBP and DBP with both the fruits and vegetables diet and the combination diet, subsequently referred to as the DASH combination diet or simply the DASH diet [318]. SBP and DBP fell more with the fruits and vegetables diet than with the control diet, by −2.8 (97.5% CI, −4.7 to −0.9) mmHg ($P < .001$) and −1.1 (97.5% CI, −2.4 to −0.3) mmHg ($P = .07$), respectively. SBP and DBP also decreased more with the combination diet than the fruits and vegetables diet, by −2.7 (97.5% CI, −4.6 to −0.9) mmHg ($P = .001$) and −1.9 (−3.3 to −0.6) mmHg ($P = .002$). These declines in BP with both experimental diets occurred within 2–3 weeks and essentially persisted throughout the rest of the 8-week study period. Thus this study indicates that a diet high in fruits and vegetables significantly reduces BP and that the addition of about three daily servings of dairy products, predominantly low-fat milk, in association with a reduced saturated and total fat intake, approximately doubled the degree of BP reduction observed with the fruits and vegetables diet.

A more recent study investigated the relationship between consuming a pattern of foods that was similar to the DASH diet and the development of end-stage renal disease (ESRD) in adults with hypertension and CKD stage 3 (estimated GFR 30–59 mL/min/1.73 m^2). Participants in the National Health and Nutrition Examination Survey (NHANES) III project were the subjects of this investigation [319]. The results indicated

TABLE 37.4 Key Nutrients in the dietary approaches to stop hypertension (DASH) diet, fruits-and-vegetables diet and Western control diet[a].

Nutrients	Western control diet	Fruits-and-vegetable diet	DASH diet
Fat (% of total kcal)	37	37	27
Saturated	16	16	6
Monounsaturated	13	13	13
Polyunsaturated	8	8	8
Carbohydrate (% of total kcal)	48	48	55
Protein (% of total kcal)	15	15	18
Cholesterol (mg/day)	300	300	150
Fiber (g/day)	9	31	31
Potassium (mg/day)	1700	4700	4700
Magnesium (mg/day)	165	500	500
Calcium (mg/day)	450	450	1240
Sodium (mg/day)[b]	3000 (130 mmol/day)	3000 (130 mmol/day)	3000 (130 mmol/day)

[a] *Values are for diets designed to provide an energy level of 2100 kcal/day.*

[b] *For the DASH-Sodium Trial the prescribed daily sodium intakes were 150 mmol (high intake, 3.45 g), 100 mmol (intermediate intake, 2.30 g) and 50 mmol (low intake, 1.15 g) [318]. An intermediate or lower sodium intake is recommended.*

Adapted from Appel LJ, et al. A clinical trial of the effects of dietary patterns on blood pressure. DASH Collaborative Research Group. N Engl J Med 1997;336:1117–24.

that, over a median follow-up period of 7.8 years, low accordance with the DASH diet was associated with an increased risk of ESRD in these people with moderate CKD and hypertension, especially if they were non-Hispanic Blacks and diabetics [319].

The DASH low-sodium diet

It is noteworthy that the DASH diet was neither a low-sodium diet nor a weight-reduction diet. The DASH-Sodium Trial was, therefore carried out to examine whether a sodium-restricted intake would have an additional BP-lowering effect in people ingesting the DASH combination diet [318]. The DASH-Sodium Trial was a multicenter study in which three different dietary sodium intakes were prescribed: a high-sodium diet, 3.45-g Na/day—roughly a typical US sodium intake; an intermediate-sodium diet, 2.3-g Na/day—a currently recommended intake; and a low sodium intake, 1.15-g Na/day. A total of 412 individuals were studied in four clinical centers [318]. Acceptance criteria included adults 22 years or older who had average SBPs of 120−159 mmHg or who had DBPs of 80−95 mmHg. Subjects first underwent a 2-week run-in period with a high-sodium Western diet. They were then randomly assigned to the DASH combination diet or to the Western diet. Both diet groups were fed each of the three levels of sodium intake for 30 days each in a randomized crossover design [318]. The primary and secondary endpoints of the study were the SBPs and DBPs with the three different sodium intakes. Statistical analyses were performed by intention-to-treat methods.

The results indicated that with the control Western diet, the intermediate sodium intake, as compared to the high intake, was associated with a reduction in SBP of −2.1 (95% CI, −3.4 to −0.8) mmHg ($P < .001$) and a reduction in DBP of −1.1 (95% CI, −1.9 to −0.2) mmHg ($P < .01$). When those individuals fed the DASH diet were fed the intermediate-sodium diet, as compared to the high-sodium diet, there was also a reduction in SBP and DBP of −1.3 (95% CI, −2.6−0.0) mmHg ($P < .05$) and −0.6 (−1.5−0.2) (P = NS), respectively. A comparison of the low versus the intermediate sodium intakes with the control Western diet indicated a further reduction in SBP of −4.6 (−5.9 to −3.2) mmHg ($P < .01$) and −2.4 (−3.3 to −1.5) mmHg ($P < .001$). The SBPs and DBPs with the DASH diet were also further reduced with the low as compared to the intermediate sodium intake by −1.7 (−3.0 to −0.4) mmHg ($P < .01$) and −1.0 (−1.9 to −0.1) mmHg ($P < .01$), respectively [318].

Perhaps most notably, these BP reductions with the DASH low-sodium diet were in addition to the BP-lowering effects of the DASH diet itself. At each level of sodium intake, the SBPs and DBPs were significantly lower with the DASH diet as compared to the control diet except for the DBP with the low-sodium diet. With the low sodium intake, the mean DBP with the DASH diet was lower than with the Western diet, but not significantly so. The BP-lowering effects of low sodium intakes were greater in the subjects who had the higher BPs than in those who were normotensive; this was observed in the individuals assigned to the control Western diet as well as in those assigned to the DASH diet. A greater reduction in BP was observed in black subjects at intermediate and low levels of sodium intake as compared to white participants [320]. Moreover, the DASH diet with reduced sodium intake lowered BP more effectively in the hypertensive participants who were older than 45 years than those who were 45 years of age or younger [320].

What is in the DASH diet that lowers blood pressure?

The answer to this question is not clear, but the following factors in the diet have been identified as possibly contributing to the lowering of BP.

Nitrate

Webb and coworkers described a possible role for nitrate in the BP-lowering effects of the DASH diet. This latter diet is high in vegetables [321,322], and vegetables contain substantial amounts of nitrate (NO_3). Ingested nitrate is absorbed from the stomach and small intestine into the circulation, where some nitrate is secreted into saliva and converted to nitrite (NO_2) by the action of bacteria on the tongue. This nitrite is then swallowed where gastric acid converts the nitrite to the vasodilator nitric oxide (NO). In one study, healthy volunteers were randomized to drink either beetroot juice, a rich source of inorganic nitrate, or water in a crossover design. After drinking beetroot juice, plasma nitrate and nitrite rose, and SBP and DBP fell by −10.4 and −8.1 mmHg, respectively [321]. The volunteers not only repeated this activity but also spit out their saliva continuously for several hours so that the nitrite would not be swallowed and thereby exposed to gastric acid. During this time, plasma nitrate again rose, but there was no rise in plasma nitrite, and SBP was significantly higher as compared to when they were allowed to swallow. Ingesting the beetroot juice and swallowing saliva also reduced endothelial dysfunction as indicated by protection against the suppression of the flow-mediated dilation of the brachial artery following ischemia/reperfusion. Finally, swallowing beetroot juice also inhibited the aggregation of platelets that were exposed to ADP or collagen [321].

Dairy products

A systematic review and metaanalysis reported that ingestion of dairy foods reduces the development of elevated BP, but this effect has been ascribed to the low-fat dairy foods but not to the high-fat dairy foods [323]. Increased intake of liquid or semiliquid dairy products (e.g., milk or yogurt) but not cheese was associated with the lower incidence of elevated BP. This difference in BP levels might be related to the sodium and potassium content of different dairy products. The higher potassium and lower sodium content of milk and other liquid dairy foods compared with cheese could explain, in part, the lack of association observed between BP and cheese consumption. The US Department of Agriculture states that two slices (1 oz) of cheddar cheese contain 210 mg of sodium, whereas one cup of milk contains 130 mg of sodium [324].

Other factors

The metabolomic composition of stored sera from the participants of the DASH study has been studied [325]. The serum concentrations of 97 compounds were significantly different in the participants when they were fed the DASH diet as compared to the control Western diet. Among these different serum concentrations, *N*-methylproline, stachdrine, tryptophan betaine, chiro-inositol, methyl glucopyranoside, and β-cryptoxanthin were significantly increased the during ingestion of the DASH diet as compared to the control Western diet, and serum theobromine, 7-methylurate, 3-methylxanthine, and 7-methylxanthine were significantly decreased. Future investigations of these compounds may reveal the mechanisms by which the DASH diet lowers BP.

The Mediterranean diet

This diet is based on the traditional foods eaten by peoples living in countries bordering the Mediterranean Sea and has been epidemiologically associated with reduced cardiovascular disease and mortality [326,327]. The diet is characterized by the daily intake of vegetables, fruits, whole grains and healthy fats, frequent consumption of fish, poultry, beans and eggs, moderate intake of dairy products, and limited intake of red meat. A recent metaanalysis of randomized and nonrandomized controlled trials investigated the effectiveness of the Mediterranean diet on BP as well as other types of diets such as the DASH diet, the low-calorie diet, the low-sodium, or the high potassium diet [328]. Metaanalyses of four trials indicated that the Mediterranean diet significantly reduced DBP (mean difference −1.81 mmHg, 95% CI −2.24, −1.38), but not SBP (mean difference −1.17 mmHg, 95% CI −2.81, 0.46) [328]. A metaanalysis of cohort and case−control studies that investigated the effectiveness of the Mediterranean diet on clinical outcomes demonstrated that people who had high Mediterranean diet scores (MDS) [186,329] had greater survival [330]. A high MDS indicates that the usual diet is similar to the Mediterranean diet. Diets like the Mediterranean diet may improve vascular function, as indicated by a greater forearm blood flow in response to a vasodilator challenge [331]. The Mediterranean diet also appears to increase vascular endothelial progenitor cells, which potentially inhibit atherosclerotic lesions in type 2 diabetic patients [332].

The mechanisms by which the Mediterranean diet lowers BP may include the following: as indicated in the DASH study, diets high in fruits and vegetables may reduce BP [317]. The BP-lowering effects of nitrate [27,322] and glutamic acid, which are present in higher amounts in vegetable proteins [211], may contribute. Moreover, the increased amounts of MUFAs and phenolic compounds due to the elevated intake of olive oil with the Mediterranean diet may also contribute to the antihypertensive effects of these high fruits and vegetables diets [333].

The PREDIMED study

The effectiveness of the Mediterranean diet was investigated in a multicenter trial in Spain, the Prevención con Dieta Mediterránea or the PREDIMED study [334,335]. This study enrolled 7447 participants with ages between 50 and 80 years old who had either type 2 diabetes or three or more major cardiovascular risk factors. The participants were randomly assigned to one of the following dietary intervention groups: a Mediterranean diet supplemented with EVOO; a Mediterranean diet supplemented with nuts; or a control low-fat diet, which was reduced in fat content and offered, each day, three or more servings each of low-fat dairy products, and bread, potatoes, pasta or rice, and two or more servings each day of vegetables. The two Mediterranean diet groups were advised to eat at least three servings per week of fish, especially fatty fish, and seafood; the low-fat diet group was encouraged to eat at least three servings per week of lean fish and seafood. All three diet groups were advised to eat at least three servings per day of fresh fruits and at least two servings per day of vegetables.

The primary endpoint was a composite of myocardial infarction, stroke, or cardiovascular death. The original results, published in 2013, indicated that the Mediterranean diet with either EVOO or nuts was associated with a better primary endpoint [334]. However, protocol deviations related to inconsistent randomization and allocation of participants to the different treatment arms were revealed later, and the original article was retracted [335]. The revised analyses without the assumption of random allocation were published in 2018 [335]. These revised analyses also indicated that the HRs for the primary endpoint were 0.69 (95% CI, 0.53−0.91) for the Mediterranean diet with EVOO and 0.72 (95% CI, 0.54−0.95) for the Mediterranean diet with nuts. These findings seem to confirm the effectiveness of the Mediterranean diet for the prevention of cardiovascular disease [336]. Several post hoc analyses of the PREDIMED study suggested that the Mediterranean diet decreases both office-measured [337] and 24-hour ambulatory BPs [338]. These antihypertensive effects of the diet may be due to the increase in nitric oxide production from ingestion of dietary nitrates and polyphenols rich in EVOO or nuts [322,339].

The PREMIER clinical trial

The DASH low-sodium diet has also been modified to add a weight loss component and other health-enhancing interventions [320]. In the PREMIER Clinical Trial, 810 participants with prehypertension or stage 1 hypertension, who had SBP of 120−159 mmHg and DBP of 80−95 mmHg, were examined as to whether these individuals can make multiple lifestyle changes that lower BP and reduce their risk factors for cardiovascular disease [106,340]. Subjects, who were mostly overweight or obese, were randomly assigned to one of three treatment groups: (1) one 30-minute counseling session on diet and physical activity, plus educational materials, but no counseling on behavioral changes (i.e., advice only); (2) an intensive behavioral intervention to achieve a set of EST healthy lifestyle goals, including weight loss, dietary sodium reduction to no more than 100 mEq/day, increased physical activity and limited alcohol intake; or (3) the EST intervention with the DASH diet (EST + DASH) [340]. Groups 2 and 3 were scheduled to have 18 counseling sessions over the 6 months of the trial.

The results of the PREMIER Trial indicated that both the EST and the EST + DASH interventions lowered SBP to a similar degree and significantly more than in the advice-only group. After subtracting the BP changes in the advice-only group, the EST and the EST + DASH intervention groups showed significant reductions at 6 months in SBP and DBP of −3.7/−1.7 and −4.3/−2.6 mmHg, respectively. The prevalence of hypertension at 6 months was similar in the two intervention groups and significantly lower than in the advice-only group. However, in the subgroup of patients with the metabolic syndrome, the EST-lowering effect on SBP was not significantly greater than with advice-only, whereas EST + DASH had a similar effect in those with and without this syndrome [341]. Moreover, the EST + DASH regimen after 6 months lowered SBP equally effectively in prehypertension and stage-1 hypertension patients who did or did not have the metabolic syndrome, whereas the EST regimen alone did not lower SBP as effectively in individuals who had the metabolic syndrome [341]. Compliance to the treatment regimens was fairly good, and the EST and EST + DASH interventions also differed significantly from the advice-only group with regard to greater weight loss, increased physical fitness, and reduced serum total cholesterol and insulin resistance [106,341]; they showed a trend toward lower urine sodium that was significant only in the EST group. Urinary sodium excretion at 6 months averaged 136.2 ± SD 64.6 and 145.6 ± 71.6 mEq/day with the EST and EST + DASH interventions, respectively.

A randomized controlled trial was conducted in Turkey involving 70 mildly hypertensive overweight or obese men and women, of whom 60 completed the trial [342]. Subjects were counseled repetitively for 3 months to follow lifestyle changes similar to those of the EST + DASH study. The knowledge conveyed in the counseling sessions addressed was the reduction of body weight, sodium intake, and alcohol intake, increased physical exercise, quitting cigarette smoking cessation, and learning stress management. The dietary recommendations were mainly based on the DASH diet. Participants in the control group were provided with routine outpatient services and were asked to maintain their usual lifestyles. Six months after the onset of the study, the interventional group showed improvements in body weight, BP, serum lipids, and lifestyle patterns.

The DASH diet also decreased the prevalence of the metabolic syndrome in other studies [343,344]. The benefits of these dietary and lifestyle interventions have been sufficiently impressive so that they have been incorporated into the recommendations for the prevention and treatment of hypertension by many national advisory groups and are included in the therapeutic lifestyle changes of the Joint National Committee (JNC) [345]. These groups now commonly recommend a DASH low-sodium type of diet along with recommendations similar to the EST lifestyle changes described earlier [345−348].

The Nordic diet

The Nordic diet consists of traditional foods originating from the Nordic countries. The nutrient content of this diet is based on the Nordic Nutrition Recommendations 2004 [349], which was also influenced by such other diets as the Mediterranean, Portfolio, DASH, and the NCEP diets. The Nordic diet is rich in fruits, berries, vegetables, legumes, low-fat dairy products, and fatty fishes that are readily obtained in Nordic countries [350]. Several clinical trials confirm the BP-lowering effects of the Nordic diet. The NORDIET trial compared the changes in BP and the lipid profiles between participants randomized to the Nordic diet and the usual Western diet. At the end of the 6 weeks of study, the SBP decreased significantly in the Nordic diet group by −6.55 ± SD13.18 mmHg compared to the change in SBP with the control Western diet (+0.60 ± 11.25 mmHg); difference between the Nordic and Western diets ($P = .008$) [350]. Another randomized study, SYSDIET, also found that after 12 weeks of intervention, ambulatory BP measurements were significantly lower in the Nordic diet group than in the control diet group, which was the isoenergetic diet with the average nutrient intake in the Nordic countries [351].

Effect of dietary sources of fuel on blood pressure

Since the DASH diet provides less fat and more protein than a typical Western diet, is it possible that these differences in fuel sources could contribute to its BP-lowering effects? As indicated earlier, amino acids and peptides derived from ingested proteins may have BP-lowering effects [204–206,209,210,213,214]. The OmniHeart study examined the relative contribution of diets providing relatively high amounts of carbohydrates, proteins, or MUFA to BP changes [8,317]. Adults with prehypertension or untreated stage 1 hypertension were randomly assigned to receive each of these three types of diets in a crossover design. The high-protein diet increased protein intake to 25% of total energy intake, and the high monounsaturated diet increased fat to 37% of total energy intake. The carbohydrate content in these latter two diets was 48% of total calories, as compared to 58% of total calories with the high-carbohydrate diet which is similar to the composition of the DASH diet. Weight was kept stable by adjusting total energy intake. The higher protein diet and the higher monounsaturated fat diet were each more effective at lowering BP as compared to the high-carbohydrate diet. Whether this was due to the lower carbohydrate intake or the higher protein or fat intake is not clear. However, these findings are consistent with observational studies indicating that higher intakes of vegetable protein or polyunsaturated fat are associated with a lower death rate from coronary heart disease and greater survival [352,353].

A metaanalysis of 10 studies comparing the effects of high carbohydrate versus high *cis*-monounsaturated fat diets also indicated that the high-carbohydrate diets were associated with slightly, but significantly higher SBP [mean difference, 2.6 mmHg (95% CI, 0.4–4.7)] and DBP [mean difference, 1.8 mmHg (95% CI, 0.01–3.6)] [354]. The same trends were noted when the analysis was restricted to six randomized crossover studies, but the results were no longer statistically significant. As indicated earlier, intake of sugar-sweetened beverages and, in people who had high urinary sodium, the amount of fructose and glucose intake was directly correlated with SBP and DBP [54,56]. It is pertinent that higher protein diets have also been associated, short-term, with improved serum lipid levels and possibly reduced insulin resistance and other metabolic benefits in patients with type 2 diabetes mellitus [355]. Recent metaanalyses, however, have not demonstrated a beneficial effect of high-protein diets on serum glucose, insulin, or HbA1c levels [355,356]. It is not yet clear whether these higher protein diets are safe or efficacious for long-term use, at least in people with limited nitrogen tolerance, such as those with CKD or liver failure [357]. They may be contraindicated in people with early CKD, as they are in persons with more advanced CKD, because of the potential risk of accelerating progressive kidney failure and also, in the latter condition, by engendering uremic toxicity. They may also be hazardous to people with liver failure and/or with genetic metabolic disorders involving the biochemical processing of urea, ammonia and the amino acids involved in their synthesis. More research into these questions would be helpful.

The amount of energy intake per se can influence the effects of sodium on BP. A post hoc analysis of the DASH study revealed that the relationship between increased sodium intake and higher BP was steeper for the participants with lower energy intakes [358]. Some authors have suggested that the recommendations for dietary sodium intake might be based on the amount of energy intake as well as the absolute amount of sodium ingested [358].

Long-term adherence and blood pressure responses to health-enhancing lifestyles

Longer term experience with the previously described clinical trials

The long-term responses to healthy diet recommendations are being examined in many studies. As indicated earlier, the HPT and Trials of Hypertension Prevention (TOHP Phase I and Phase II), in which patients were counseled on weight-reduction and/or sodium-reduction diets for up to 4 years, indicated that there was a progressive loss of adherence to these dietary intakes [310,314–316]. TOHP Phase I also indicated a reduced OR of developing hypertension 7 years after the onset of the trial, in the people in the weight reduction group (OR 0.23; 95% CI, 0.07, 0.76; $P = .02$) [359]. The incidence of hypertension tended to be lower in the sodium reduction group but this difference was not significant (OR 0.65; 95% CI, 0.25, 1.69; $P = .37$) [359]. The HPT and TOHP Phase II trials also demonstrated that some antihypertensive effects remained 3 or 4 years after the onset of the trial [310,314–316].

In the PREMIER Clinical Trial, participants, who were originally followed for 6 months, were then monitored for an additional 12 months during which the advice-only group underwent one additional 30-minute counseling session and received educational materials; the EST intervention and EST intervention + DASH diet groups attended monthly group sessions and three individual counseling sessions and were asked to keep food diaries, monitor their dietary energy and sodium intake, and record the minutes of physical activity. At 18 months after the onset of the PREMIER Trial, the EST intervention and EST intervention + DASH diet groups, in comparison to the advice-only group, each showed greater weight losses of −2.2 and −2.7 kg, respectively ($P < .01$ for each group), and significantly lower energy intakes [360]. Precisely 25% of both EST intervention groups attained the target weight loss goal of −6.8 kg. Urinary sodium excretion was also significantly lower in both intervention groups as compared to the advice-only group, by −16.7-mmol sodium and −15.4-mmol sodium, respectively. Compared to the advice-only group, the OR for hypertension was 0.83 and 0.77, respectively, in the EST and EST + DASH groups at 18 months and was significantly lower only in the EST + DASH group. Among people who were hypertensive at baseline, the OR for remaining hypertensive was significantly lower in both intervention groups as compared to the advice-only group. However, the change in BP levels at 18 months was not different among the three groups. This might be due to the reduction of antihypertensive medications. The ORs of being on antihypertensive medications compared to the advice-only group were 0.57 (95% CI 0.41, 0.81) and 0.62 (95% CI 0.45, 0.85) in the EST and EST + DASH diet groups, respectively, at the end of 18 months.

Other longer term studies on diet, adherence, and blood pressure

Folsom et al. employed a DASH diet index score to evaluate the long-term consequences in nonhypertensive participants in the Iowa Women's Health Study who ingested diets with food patterns similar to the DASH diet [361]. Adjusting for age and energy intake, they found that greater adherence to a DASH-type diet was associated with a lower incidence of hypertension and cardiovascular mortality, but these associations were not statistically significant after adjustment for other risk factors. However, these women were assessed while they ingested their usual intakes, and they did not undergo specific training and follow-up with regard to adherence to the DASH diet.

The WHI Dietary Modification Trial evaluated the effect of intensive behavioral modification to ingest a diet of increased fruits, vegetables, and whole grains and reduced fat on BP and other clinical outcomes, including cardiovascular events [362]. A total of 48,835 postmenopausal women were randomized to this treatment or to receive dietary educational materials. They were followed for a mean of 8.1 years. The primary aim of this study was to assess reduction in the incidence of breast and colorectal cancers. The diet was not specifically designed to lower sodium or energy intake, although there was a small decrease in energy intake and body weight in the treatment versus the control group. Although the intake of all dietary components changed in the prescribed direction, SBP did not change significantly, and there was a significant but very modest (−0.31 mmHg) reduction in DBP. Moreover, there was no reduction in the incidence of coronary heart disease, stroke, or all cardiovascular events with this diet.

The DEW-IT study was a 9-week intensive healthy lifestyle modification intervention that evaluated a low-energy version of the DASH diet and a nonactive interventional arm in 44 overweight and obese hypertensive patients [363]. There was significantly greater weight loss with the lifestyle intervention at the end of the 2-month period. However, at 1 year of follow-up, the weight loss group had regained almost all of their lost weight, and their weight change was not different from the nonintervention group [364].

The ADAPT study evaluated changes in lifestyle and clinical characteristics in 241 overweight or obese hypertensive adults after they were randomized to UC or an intensive program of lifestyle counseling [365,366]. At 4 months into the study, which was at the end of the 4-month interventional period, and at 16 months, which was the end of the 12-month period of follow-up, there was significantly greater weight loss associated with a more healthy dietary intake in the lifestyle changes group. Ambulatory BP was lower at 4 months after starting counseling but not after the 1-year follow-up [365]. Three years after completion of the first 4-month intervention period in the original study, that is, after an additional 2 years of follow-up, the relative improvements in the lifestyle group, as compared to UC, were limited to increased physical activity, some food intakes, and a minor decrease in serum cholesterol, but no difference in weight loss, BP, changes in antihypertensive medications, or other risk factors [367].

Other lifestyle modification programs also report that initial weight losses are not maintained long term [368]. However, Viera et al. evaluated adults who had participated in a survey and who indicated that they had been told they were hypertensive [369]. Those adults who also stated that they were advised on lifestyle changes were significantly more likely to describe healthy changes in lifestyle (e.g., changed eating habits, including reduced salt and alcohol intake or exercise) than those who did not recall being advised on lifestyle changes. It is emphasized that these data were obtained from participant reports.

Remote counseling using communications technology

More recent studies investigated the effectiveness of promoting participant adherence with the use of information and communications technology. The TEXT ME study was a single-blind, randomized clinical trial that included 710 patients with proven coronary heart disease [370]. The intervention group received four text messages regarding healthy lifestyle habits, including at least one message per week focusing on diet, in addition to standard care, whereas the control group received standard care. The outcome of this study was adherence to eight Australian dietary guidelines, that is, consumption of vegetables, fruits, oils, spreads, fish, takeaway food, salt, and standard alcohol drinks. The participants received four text messages per week over a period or 6 months with at least one per week focusing on diet. The proportion of the participants who adhered to four or more dietary recommendations was significantly higher (93%) in the text message group than in the control group (75%, relative risk, 1.23, 95% CI, 1.15–1.31, $P < .001$) [370].

Another randomized controlled study investigated the effectiveness of short message systems regarding healthy diet, medication, and smoking cessation on adherence to these measures [371]. Adherence was assessed by the Mediterranean Diet Adherence Screener, Medication Adherence Scale, and Readiness to Quit Ladder. The participants demonstrated a higher adherence to the Mediterranean diet ($P < .001$) and medication ($P = .001$), whereas no difference was found in terms of smoking. It should be noted that these last two studies had short observational periods, that is, 6 [370] and 3 months [371], respectively. The effectiveness of these interventions over longer periods of time needs to be investigated.

Friedberg et al. conducted a randomized prospective controlled trial of 533 adults who had repeated BP measurements over 6 or more months indicating poorly controlled BP despite being prescribed antihypertensive drugs [372]. These investigators evaluated the effectiveness on BP control of either stage-matched intervention (SMI) or nontailored health education intervention (HEI) as compared to UC treatment. Patients in SMI received tailored monthly phone counseling for exercise, diet, and medications based on their current stage of change which was assessed by asking them a set of validated stage-of-change questions. The HEI group received nontailored monthly telephone counseling of standard information concerning hypertension, diet, medication, and exercise. After 6 months, BP control (defined as BP < 130/80 mmHg for diabetic or CKD patients, BP < 140/90 mmHg for other patients) was attained in 64.6% of the SMI participants ($P = .001$ vs UC group), 54.3% of the HEI patients ($P = .108$ vs UC), and 45.8% of the UC group. Moreover, changes from baseline in the DASH diet score were only significant in the SMI group ($P = .013$), but not in the HEI group ($P = .318$), as compared to the UC group [372]. These findings reinforce the importance of individualizing the approach to each patient to maximize adherence to healthy lifestyles, including healthy diets, and to control BP.

Challenges to diet and lifestyle approaches for preventing and treating hypertension

Other researchers report rather mediocre long-term (i.e., more than 6–24 months) adherence to these foregoing dietary regimens. Adherence to diet prescription and weight loss, although often statistically significantly better than baseline or than the control diets, were often small [360,373]. For example, many obese patients have 15, 25, or more kg of excess body fat. Dietary weight reduction programs are often considered rather successful if the participant loses 5 or 6 kg over the long term. It is possible, of course, that a disproportionately healthy benefit may be obtained with these rather modest fat losses by obese patients.

This dilemma may be more problematic serious for some ethnic groups that, studies indicate, may have greater difficulty adhering to some components of the DASH diet [374,375]. Examination of the NHANES data for the years 1999–2004 indicates that only 19.4 ± 1.2(SEM)% of 4386 people with known hypertension had a diet similar to the DASH diet [376]. These values are substantially lower than the proportion of known hypertensives who were accordant with the DASH diet (26.7% ± 1.1%) in the NHANES data for 1988–94 [376]. Indeed, the NHANES data indicate that adherence to healthy lifestyles appears to be diminishing in the United States [377]. Although at least most of the NHANES participants probably had not been trained in the importance of or the preparation of the DASH diet, the principles of the DASH diet have been recommended in guidelines promoted by the JNC on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure and other health and health-care organizations for many years [3,378–380]. Large numbers of Americans are now counseled in healthy lifestyle modifications, although some population groups are less commonly counseled, particularly the young, perhaps the less educated, and people with low cardiovascular risk factors [341].

Thus the results concerning adherence to the DASH or other dietary prescriptions to reduce BP or cardiovascular events are somewhat conflicting. As pointed out by Logan [381], there are several possible explanations for the differences in adherence to these diets. The DASH trial was short-term, and all food was prepared in research kitchens and provided to the subjects at no cost. Moreover, on weekdays either lunch or supper meals were eaten in a research unit [317,382]. In contrast, in other studies, the food had to be purchased and prepared by the participants. When food must be purchased and prepared for long or indefinite periods of time by the consumer who is not participating in an intensively controlled research protocol, adherence may fall. Another question concerns the cost-effectiveness of long-term counseling to maintain adherence to healthy lifestyles and diets. In some centers, counseling has been done by health-care workers who are more expensive. People who are not such professional health-care workers, as dietitians or nurses, can be trained rather quickly to become effective lifestyle coaches [383].

Long-term remote counseling for weight reduction by telephone, a program-specific web site, and email was examined as a strategy for effectively promoting weight reduction at greater efficiency and less cost (please also refer to the “Remote counseling using communications technology” section) [384]. Primary care providers played a supportive role in the program but were not directly involved in the interventions. In this latter trial, one group of obese participants received exclusively remote but frequent counseling; another group received a combination of incenter person-to-person counseling plus three remote counseling sessions [384]. A third group served as controls. At 24 months, weight loss averaged −0.8 kg in the control group, −4.6 kg in the group receiving remote counseling ($P<.001$ vs controls), and −5.1 kg in the group receiving direct person plus remote counseling ($P<.001$ vs controls). Thus a combination of employing trained laypeople as counselors plus the use of remote counseling may substantially reduce the costs of diet and lifestyle-induced weight loss programs, especially if the techniques for weight reduction can be made more effective.

The use of bariatric surgery to control obesity and its adverse consequences may be an important adjunct to dietary measures to control hypertension and reduce cardiovascular risk (see Chapter 40: Nutritional and Metabolic Management of Obesity and The Metabolic Syndrome in Patients with Chronic Kidney Diseaseand Chapter 41: Bariatric Surgery and Kidney Disease). The long-term, multiyear benefits to people who adhere closely to the DASH or DASH low-sodium diets also are not yet known, although it seems reasonable to believe that these diets and lifestyle changes will be healthy indefinitely [385]. Moreover, it is not entirely clear that these diets are similarly effective for all racial, ethnic, and age groups and whether there are certain morbid conditions for which these diets may not be beneficial. In both DASH studies, the potassium content of the control diet was below the 25th percentile of the estimated usual potassium intake in the United States [381]. Moreover, most of the DASH study patients were African-American [317], a population whose BP is particularly potassium-sensitive and who may require a high potassium intake in the range of the DASH diet to avoid sodium sensitivity induced by potassium deficiency [145]. Thus these results may not be as applicable to non-African-Americans or to people who are already ingesting higher potassium diets. On the other hand, the large-scale, observational, multiyear Nurses’ Health Study II indicated that those individuals who followed a low-risk diet and low-risk lifestyle had a lower self-reported incidence of hypertension [386]. It is relevant and encouraging that the demonstrated BP-lowering effects of healthy dietary regimens and lifestyles coupled with difficulty in adherence has provided a commercial incentive to develop functional foods and nutraceuticals that may provide recommended nutrients [387]. Hopefully, these products will enhance the ability of people to follow the recommended dietary guidelines.

Exercise

Exercise training and its physiological, metabolic, and clinical consequences are discussed in Chapter 51: Exercise Training for Individuals With Advanced Chronic Kidney Disease. Some but not all studies of exercise and BP suggest that regular exercise training may reduce BP. Aerobic exercise training and resistance training are reported to decrease BP in prehypertensive and stage 1 hypertensive individuals and may lower serum cholesterol, particularly when combined with a low-fat intake [388]. Exercise may also accelerate weight reduction in obese individuals who are ingesting a low-calorie diet [389]. A cohort of 3148 healthy adults underwent studies of cardiorespiratory fitness, determined by treadmill exercise, which was measured over a 6-year interval of time [21]. Improvement in cardiorespiratory fitness was associated with a reduction in the incidence of hypertension, the metabolic syndrome, and hypercholesterolemia. A gain in the percent body fat or BMI was each associated with an increased incidence of hypertension, metabolic syndrome, and hypercholesterolemia [21].

The Exercise and Nutrition interventions for CardiOvasculaR hEalth study investigated the combined effects of the DASH diet and exercise to reduce body weight [390]. The study randomly assigned 144 patients with SBP of 130−159 mmHg or DBP of 85−99 mmHg to the original DASH diet alone (DASH-A), the DASH diet combined with a behavioral weight management program that included a supervised aerobic exercise training program three times per week for 30 minutes per session

(DASH-WM), and the usual diet control (UC) in which the participants maintained their usual dietary and exercise habits. After a 4-month period of intervention, the clinic-measured BP levels, ambulatory BP levels, and body weights were significantly lower in the DASH-WM group as compared to the DASH-A and UC groups [390]. The results of this study further support a significant role for exercise and body weight reduction for lowering BP.

Two mechanisms by which regular physical exercise may lower BP include a reduction in oxidative stress and amelioration of insulin resistance and its consequent hyperinsulinemia [391]. In the presence of oxidative stress, 8-Iso-PGF2α, a potent vasoconstrictor, is produced [391]. Insulin resistance with hyperinsulinemia impairs NO synthesis, which will predispose to hypertension.

It is important to remember that the transient increase in BP that occurs when normal people exercise may be greatly exaggerated in hypertensive individuals. Thus BP should be monitored carefully in hypertensive persons who are embarking on exercise training, until it is ascertained that dangerous increases in BP do not occur [392].

Anorexigenic medicines

Many anorexigenic medicines have been evaluated for their effects on promoting fat loss in overweight or obese people. Studies indicate that a reduction in BP may accompany weight loss [301,393,394]. Most of these drugs have been abandoned because of adverse side effects. One anorexigenic agent still in use is orlistat, a lipase inhibitor that reduces intestinal fat absorption. Orlistat induces weight loss more effectively than placebo treatment, on average by roughly 4 kg (mean difference −3.73; 95% CI, −4.65, −2.80) [394]. Orlistat may cause disturbing gastrointestinal symptoms of flatulence, bloating, abdominal pain, and diarrhea [393]. Treatment with orlistat also lowers BP [301,395]. In a metaanalysis, there was a statistically significant reduction in SBP and DBP with orlistat of −2.5 and −1.9 mmHg, respectively [395].

Phentermine–topiramate and naltrexone–bupropion are two other medications that are prescribed for body weight reduction in patients with morbid obesity. Phentermine is a central norepinephrine-releasing drug, which was approved in 1959 and remains a popular anti-obesity drug in the United States. Topiramate has several pharmacological mechanisms of action and is prescribed for epilepsy and migraine prophylaxis. However, Topiramate has dose-dependent neuropsychiatric adverse events, including memory impairment and mood alterations, including depression, which impeded its use as monotherapy for obesity [396].

The combination of these two drugs was tested for the treatment of obesity and hypertension. A 56-week phase 3 trial recruited 2487 patients with BMI of 27–45 kg/m^2 and two or more of the following comorbidities: hypertension, dyslipidemia, diabetes or prediabetes, or abdominal obesity. Patients were randomly assigned to receive a placebo, once-daily phentermine, 7.5 mg, plus topiramate, 46.0 mg, or once-daily phentermine, 15.0 mg, plus topiramate, 92.0 mg, in a 2:1:2 ratio [396]. At 56 weeks the change in body weight was −1.2% (95% CI, −1.8, −0.7), −7.8% (95% CI, −8.5, −7.1, $P < .0001$), and −9.8% (95% CI, −10.4, −9.3; $P < .0001$) in the patients assigned to placebo, once-daily phentermine 7.5 mg plus topiramate 46.0 mg, or once-daily phentermine 15.0 mg plus topiramate 92.0 mg, respectively.

The group assigned to phentermine–topiramate experienced significant decreases in SBP and DBP. Changes in SBP from baseline to week 56 were −2.4 mmHg (95% CI, −3.3, −1.5), −4.7 mmHg (95% CI, −5.9, −3.5; $P = .0008$), and −5.6 mmHg (95% CI, −6.5, −4.6; $P < .0001$) in the patients assigned to placebo, once-daily phentermine 7.5 mg plus topiramate 46.0 mg, or once-daily phentermine 15.0 mg plus topiramate 92.0 mg, respectively. Changes in DBP from baseline to week 56 were −2.7 mmHg (95% CI, −3.3, −2.1), −3.4 mmHg (95% CI, −4.2, −2.6; $P = .1281$), and −3.8 mmHg (95% CI, −4.4, −3.2; $P = .031$) in the patients assigned to placebo, once-daily phentermine 7.5 mg plus topiramate 46.0 mg, or once-daily phentermine 15.0 mg plus topiramate 92.0 mg, respectively. Common adverse events with this drug combination were dry mouth, paresthesia, constipation, insomnia, dizziness, and dysgeusia. Due to adverse events, 89, 58, and 192 participants, respectively, discontinued their assigned intervention out of 994, 498, and 995 persons assigned to placebo, phentermine 7.5 mg plus topiramate 46.0 mg, and phentermine 15.0 mg plus topiramate 92.0 mg, respectively.

Combined treatment with sustained-release naltrexone and bupropion was developed to stimulate the hypothalamic proopiomelanocortin neurons with bupropion while simultaneously blocking opioid-mediated proopiomelanocortin autoinhibition with naltrexone. Naltrexone and bupropion are prescribed for addictive disorders. These drugs synergistically modulate the mesolimbic reward pathways and reduce food intake. A 56-week study was conducted in 1742 participants who had a BMI of 30–45 kg/m^2 with uncomplicated obesity or a BMI of 27–45 kg/m^2 and controlled hypertension and/or dyslipidemia [397]. Study subjects were randomly assigned in a 1:1:1 ratio to receive sustained-release naltrexone, 32 mg/day plus sustained-release bupropion 360 mg/day combined in fixed-dose tablets (NB32), sustained-release naltrexone 16 mg/day plus sustained-release bupropion 360 mg/day combined in fixed-dose tablets (NB16), or placebo twice a day. Naltrexone–bupropion at both doses was associated with a significantly reduced body weight at the end of the 56-week period, but neither dose of these medicines had a significant effect on SBP or DBP [397].

Conclusion and recommendations

Many studies indicate that nutritional intake and nutritional status have a major effect on the probability of developing hypertension and on the severity of hypertension in the general population. Appropriate dietary management may prevent the onset of hypertension and eradicate or improve mild hypertension in many people. Diets can be a useful adjunct to pharmacological therapy for the treatment of more severe, EST hypertension. Key nutritional elements that prevent or ameliorate hypertension include the prevention or treatment of obesity, the low-sodium DASH diet, adequate potassium intake, and possibly sufficient intake of fish oil, magnesium, and certain types of tea. Dietary intake or avoidance of certain other nutrients may also affect the incidence or severity of hypertension. Some evidence indicates that regular exercise may reduce resting BP; exercise, of course, has other health-enhancing advantages. A dietary approach to either prevent or treat hypertension is indicated in Table 37.5. For patients who have a major elevation in BP, it is very uncommon for their hypertension to respond adequately to dietary management alone. These individuals will almost certainly also require medicines to control their hypertension, but dietary control may still improve the ease with which their elevated BP may be managed.

TABLE 37.5 A suggested dietary approach to prevent or treat hypertension[a,b] [399].

1. Maintain desirable body weight
2. Use the DASH diet (a diet high in fruits, vegetables, and low-fat dairy products and low in saturated and total fat)
3. Limit daily NaCl consumption to 5.85 g/day (2.30 g of sodium/day) or lower
4. Maintain adequate potassium and magnesium intake
5. Recommended calcium intake for noncalcium stone formers (about 1000 mg/day for persons aged 19–50 years and 1200 mg/day for persons ≥ 50 years)
6. For individuals who drink alcohol, no more than two drinks (3–4 units[c])/day
7. Consider a high omega-3 fatty acid diet (i.e., about 3–6 g/day of fish oil/day)

[a] *For persons with a chronic illness, each of these recommendations should be reviewed with his/her physician to ensure that it is compatible with their medical management.*
[b] *Regular (approximately daily) exercise activity is also recommended.*
[c] *One unit contains 10 mL or 8 g of pure alcohol. This measure is used in the United Kingdom.*
DASH, Dietary approaches to stop hypertension.

Individuals who are obese or have other dietary habits that may predispose to hypertension (e.g., high sodium chloride intake) should be encouraged to inaugurate appropriate dietary therapy. If the BP is substantially elevated, a reasonable approach would be to start pharmacological antihypertensive therapy concomitantly with dietary management. If the patient is committed to dietary therapy of hypertension, he or she may do the following. Once the BP has stabilized at the target level, attempts may be made to gradually withdraw the antihypertensive medicines while maintaining strict dietary management. Exercise training should be encouraged, but only after careful medical evaluation of cardiovascular and hemodynamic activity, including any excessive rise in BP in response to exercise of persons who have hypertension, who are older, or who have major underlying illnesses, such as heart disease or kidney disease.

Ultimately, the most effective behavioral approach to prevent or ameliorate hypertension is by the development of a healthy lifestyle that includes a DASH, low sodium–type diet or Mediterranean-type diet, regular physical exercise, and intake and avoidance, respectively, of those nutrients that appear to lower or increase BP (see Table 37.2).

Key points

1. Obesity is one of the main nutritional predisposing factors to hypertension.
2. The many mechanisms by which obesity and excessive energy intake predispose to hypertension include increased activity of the renin–angiotensin–aldosterone system, probably a rise in nonaldosterone-mediated mineral corticoid activity, increased sympathetic nervous system activity, insulin resistance, salt-sensitive hypertension, excess salt intake, and the reduced kidney function which is often present in obese individuals.
3. High sodium chloride intake is the other main nutritional predisposing factor to hypertension.
4. Increasing potassium intake, particularly in people with potassium-deficient intakes, may lower BP and reduce the risk of hypertension.
5. Higher intakes of polyunsaturated fatty acids, protein, and possibly certain amino acids, vitamin D, and green coffee bean extract may lower blood pressure (BP).
6. Some evidence suggests that dark chocolate, but not white chocolate, and oolong, green, black, and sour tea may reduce the risk of hypertension. Evidence suggests that excessive energy intake,

sugar-sweetened beverages, fructose, and glucose may raise BP.

7. Large alcohol intakes may increase the risk of hypertension and acutely and chronically raise BP. Some evidence indicates that consumption of low-to-moderate amounts of alcohol may raise BP in African-American men but not in white men or women or African-American women.
8. Certain diets and lifestyle changes, including regular exercise, appear to lower BP in people with prehypertension or mild hypertension and prevent the development of hypertension.
9. The dietary approaches to stop hypertension low-sodium diet, which is high in fruits and vegetables, low-fat dairy products, potassium, magnesium, calcium, and fiber, and low in saturated fatty acids, total fat, and sodium, is such a diet.
10. Long-term adherence to healthy, BP-lowering diets is difficult for many people to attain, and methods for obtaining long-term adherence to such diets and healthy lifestyles continue to be investigated.
11. Bariatric surgical procedures in association with counseling for healthy lifestyle changes appear at present to be the most effective and reliable methods for long-term, major reductions in body fat.

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CHAPTER

38

Nutrition and anemia in chronic kidney disease

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Prevalence and importance of anemia in chronic kidney disease

Anemia is a frequent complication in chronic kidney disease (CKD) and reflects the severity of CKD. Data from the National Health and Nutrition Examination Survey 2007–10 estimated that 14.0% of the US population had CKD. Anemia, defined as hemoglobin (Hb) levels ≤ 12 g/dL in women and ≤ 13 g/dL in men, was twice as prevalent in people with CKD (15.4%) as in the general population (7.6%). Furthermore, the prevalence of anemia increased with increasing CKD severity, from 8.4% at stage 1 to 53.4% at stage 5 [1]. In a more recent retrospective analysis based on the United States (US) Veterans Administration, of nearly a million US adult with CKD, 20.6% had anemia and 30% had absolute iron deficiency and 19% had functional iron deficiency [2]. Very high (≥ 17 g/dL) or reduced (<13 g/dL) Hb levels and CKD were independently predictive of substantially increased risks of death and hospitalization for heart failure [3].

Causes of anemia in CKD

Many factors contribute to anemia in CKD, a major cause of which is reduction in erythropoietin (EPO) production by the failing kidneys. Iron deficiency, worsening uremia, inflammation, loss of residual kidney function, nutritional deficiencies of folate or vitamin B12, and severe hyperparathyroidism are other important factors for anemia in CKD.

Mechanisms of anemia and hypoxia-inducible factor pathway in CKD

EPO is predominantly produced by the kidneys and acts on erythroid cells expressing EPO receptors, controlling their proliferation, differentiation, and survival [4]. Fibroblasts in the renal cortex and outer medulla are the principal cells that produce erythropoietin in response to hypoxia or anemia [5]. The EPO gene is regulated by hypoxia through the hypoxia-inducible factor (HIF) system discovered in 1992 and is a family of heterodimeriic transcription factors, including HIF-1α, HIF-2α, and HIF-3α subunits that are oxygen dependent and the HIF-1β and HIF-2β subunits that are constitutively expressed. In normal oxygen conditions, HIF-1α subunits are hydrolyzed in specific proline residues by propyl-4-hydroxylase domain (PHD), becoming a target for ubiquitination by von Hippel–Lindau tumor suppressor protein and thus subjected to proteosomal degradation. Under hypoxic conditions, as PHD proteins that require oxygen for hydroxylation of HIF-1α subunits are inhibited, HIF-1α is not degraded to the same extent. The stabilized HIF-1α subunits translocate into the nucleus and heterodimerize with HIF-1β subunits, thus activating hypoxia response genes that encode for synthesis of EPO, EPO receptor, transferrin receptors, vascular endothelial growth factor (VEGF), and glycolytic enzymes, stimulating erythropoiesis, iron availability, and angiogenesis [6].

The kidneys respond to hypoxia or anemia by increasing the number of renal erythropoietin-producing cells (REPCs) that are sensitive to changes in oxygen tension, thus increases EPO production. In face of renal injury or proinflammatory stimuli, the REPCs transdifferentiate into myofibroblasts that lead to extracellular matrix accumulation, collagen production, and renal fibrosis and impair EPO production [7]. Activation of HIFs selectively by genetically inactivating HIF prolyl hydroxylases (PHD1, PHD2, and PHD3) in REPCs would reactivate EPO production in myofibroblast-transdifferentiated REPCs. Notably, combined deletions of PHD1 and PHD3 genes prevented loss of EPO production without causing polycythemia. Loss of PHD2 restored EPO gene expression in injured kidneys but caused polycythemia.

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Thus activation of HIF signaling by reactivating EPO production in MT-REPCs is an attractive therapeutic strategy for treating renal anemia [7]. In vivo knockout studies showed that HIF-2α but not HIF-1α is the primary regulator of hypoxic EPO induction in both the kidneys and the liver. Mutations that activate HIF-2α can result in erythrocytosis. Further evidence from cell culture studies suggest that PHD2 serves as the critical oxygen sensor that regulated HIF-2α upstream stimulation of EPO [8]. However, the role of oxygen sensor PHDs differs between both organs in EPO production. REPCs predominantly use PHD2 and liver cells use all three PHD isoforms equally for degrading HIF-2α while hepatocytes use all three PHD isoforms equally for degrading HIF-2α.

Iron homeostasis

Dietary ferric iron is first reduced to ferrous iron by duodenal cytochrome B (DCytoB). Ferrous iron is transported into enterocytes lining the gut via divalent metal transporter 1 (DMT1). Transport of ferrous iron out of enterocytes into bloodstream occurs via the iron transporter ferroportin. Once in the bloodstream, ferrous iron is oxidized to ferric iron by ceruloplasmin and is bound to transferrin for transport. Transferrin binds to cellular membrane transferrin receptor 1 (TFR1) and iron is internalized by endocytosis. The utilization of iron is opposed by hepatic peptide hormone hepcidin that is a key regulator of iron availability (Fig. 38.1). Hepcidin is a peptide discovered in the 21st century with a molecular size of 2.7 kD. It is not strongly bound to plasma proteins and is rapidly cleared by the normal kidneys where it is largely reabsorbed and degraded by the proximal tubules. A small proportion of hepcidin escapes this mechanism and can be detected in urine [9], where daily excretion is approximately proportional to serum hepcidin concentrations [10]. Hepcidin is a "hypoferremia"-inducing hormone. It reduces dietary iron absorption from the intestine and blocks release of stored iron both from the macrophages and from the liver by inhibiting

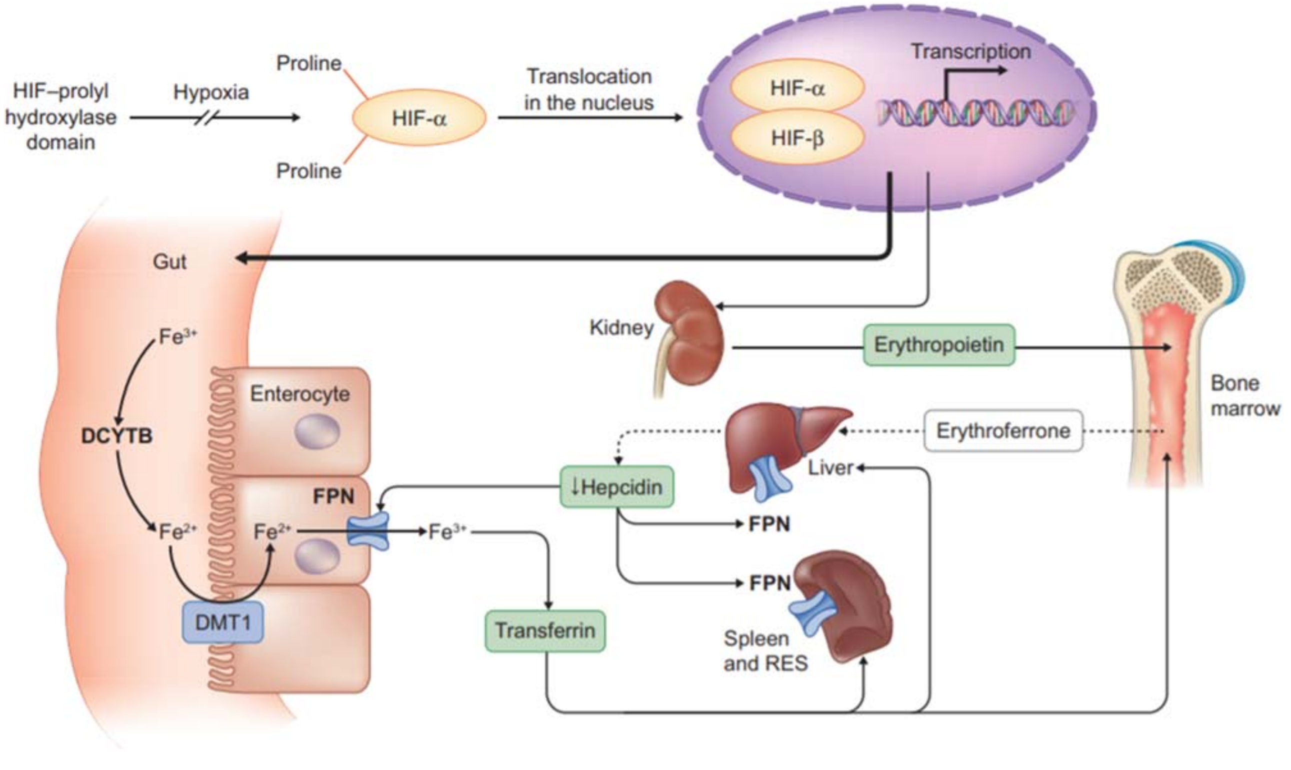

FIGURE 38.1 Iron metabolism and hypoxia-inducible factor prolyl hydroxylase domain transcription pathway in response to hypoxia or anemia. Under hypoxic conditions the HIF prolyl-4-hydroxylase domain does not inactivate HIF-α that translocates into the nucleus and after dimerization with HIF-β activates transcription of EPO in the kidney and in the liver, which stimulates erythropoiesis in the bone marrow. HIF synchronizes EPO production with iron metabolism by stimulating duodenal cytochrome B reductase 1, which reduces $Fe^{3þ}$ to $Fe^{2þ}$ and divalent metal transporter 1, which allows iron transport into the enterocyte. Iron is then released into the circulation via FPN, which is also HIF inducible. In the circulation, iron is transported in a complex with transferrin to the reticuloendothelial system in the liver and in the spleen to be stored in the ferritin and to the bone marrow for erythropoiesis. Transferrin also is HIF regulated. Increased erythropoiesis in the bone marrow produces erythroferrone, which suppresses hepcidin in hepatocytes. Hepcidin suppression increases FPN expression on enterocytes, hepatocytes, and macrophages, resulting in increased iron absorption and mobilization from internal stores. *EPO*, Erythropoietin; *FPN*, ferroportin; *HIF*, hypoxia-inducible factor. *Reprinted with permission from Locatelli F, Del Vecchio L, De Nicola L, Minutolo R. Are all erythropoiesis-stimulating agents created equal?* Nephrol Dial Transplant *2020. Mar 24:gfaa034. doi: 10.1093/ndt/gfaa034. Online ahead of print.Ref 65 in this paper.*

ferroportin [11]. It thus reduces the availability of stored iron, makes anemia worse, and could contribute to erythropoiesis resistance or restriction. In situation of infection and inflammation, hepcidin levels are upregulated by proinflammatory cytokines, interleukin-6, its receptor, and JAK2-Stat 3 pathway, causing hypoferremia and worsening anemia [12]. This response has a host defense function for siderophilic bacteria of which the pathogenicity is enhanced by iron. Conversely, hypoxia and erythropoiesis stimulator such as erythropoietin-stimulating agent (ESA) negatively regulate hepcidin production and downregulation of hepcidin allows enhanced iron mobilization from the body stores and availability for erythropoiesis (Table 38.1).

HIF pathway and iron homeostasis

The HIF pathway also regulates iron homeostasis to meet the iron demands of erythropoiesis via direct and indirect mechanisms. HIF modulates iron handling by upregulating transferrin, TFR1, and ceruloplasmin, allowing greater transport of iron to tissues and increasing intestinal absorption of iron via upregulation of DCytoB and DMT1 and downregulation of hepcidin [13]. HIF-mediated regulation of hepcidin is dependent on EPO-stimulated erythropoiesis. HIF-2 upregulates ferroportin during iron deficiency in the small intestine and increases the capacity of basal iron transport. HIF-2 activation in the small intestine binds to hypoxia response elements of apical iron absorption genes.

TABLE 38.1 Factors regulating hepcidin expression.

Factors upregulate hepcidin	Factors downregulate hepcidin
• Inflammation	• Hypoxia
• Infection	• Decreased hepatic iron
• Intravenous iron administration	• Decreased TSAT
• Increased hepatic iron	• Testosterone
• Increased TSAT	• Pregnancy

TSAT, Transferrin saturation.

Altered iron balance and iron homeostasis in CKD

Iron is a vital component of human cellular physiology. Under physiologic conditions, iron is regulated in a closed system, with 1–2 mg/day iron absorbed to balance the iron lost [14]. Total body iron content is approximately 2–5 g and is much higher than the daily turnover (Fig. 38.2). Ferroportin, the transmembrane efflux channel, serves as the exporter of iron from enterocytes, macrophages, and hepatocytes. Patients with CKD, especially those on dialysis, showed marked alterations in iron balance and tissue iron distribution because of reduced iron absorption, increased iron losses, and impaired utilization of iron from body stores, thus giving rise to anemia. The amount of gastrointestinal blood loss was estimated at least three times higher in CKD patients and six times higher in dialysis patients than in non-CKD controls [15,16]. Patients on hemodialysis (HD) experienced

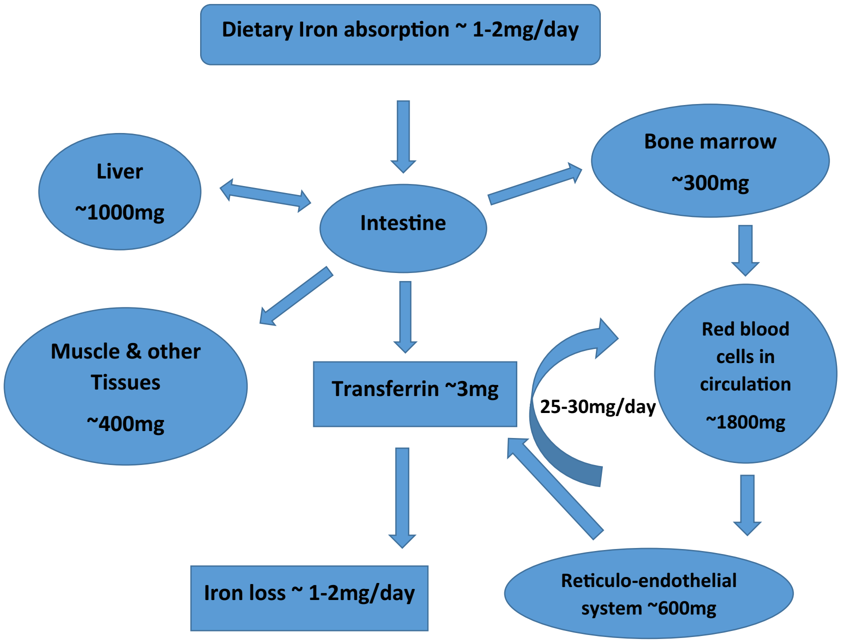

FIGURE 38.2 Iron homeostasis in health subject. Values in figure are estimations and may vary between subjects.

higher blood loss due to the HD procedure itself and from the blood draws. Total blood loss may, on average, amount to 2–5 L/year, corresponding to 0.8- to 2.0-g iron loss [15,17]. There are some suggestions that long-term HD patients may, on average, lose 2- to 3-g iron per year (including physiologic iron loss) (Fig. 38.3).

Patients with CKD also have reduced dietary iron intake and absorption. Decreased protein intake due to poor appetite with implementation of low-protein diets may result in reduced iron availability for absorption. Some medications may inhibit iron absorption from the gut such as proton pump inhibitors. CKD patients also exhibit reduced availability of stored iron as hepcidin levels are greatly increased. Hepcidin levels of CKD subjects and those on HD were reported to be three- to fivefold higher and may be up to ninefold higher compared with healthy controls. Hepcidin levels in CKD patients may increase due to chronic inflammation, infections, or reduced renal clearance of hepcidin. The increased hepcidin levels reduced iron availability and mobilization from storage and may explain resistance to ESA treatment or restricted erythropoiesis.

Evaluation of iron status in CKD

According to KDIGO 2012 Clinical Practice Guideline, initial evaluation of anemia in all anemic CKD patients should include assessing serum transferrin saturation (TSAT) and serum ferritin level and address all correctable causes of anemia, including iron deficiency prior to initiation of ESA therapy (not graded). KDIGO suggested iron status (TSAT and serum ferritin) be evaluated at least every 3 months during ESA therapy, including the decisions to start or continue iron therapy (not graded). Iron status may be evaluated more frequently when initiating or increasing ESA dose, blood loss or when monitoring response after a course of intravenous (IV) iron and in other circumstances where iron stores may become depleted (not graded) [18]. However, there are limitations with current tests used to assess body iron stores or status.

Transferrin

Transferrin is a negative acute-phase reactant. Transferrin level and TSAT are affected by coexistent infection, inflammation, malnutrition, malignancy, progesterone, or recent iron intake [19]. TSAT should be measured in the morning after an overnight fast to reduce diurnal variation and at least 1 week after high-dose IV iron to avoid spurious elevations [20].

Ferritin

Although low serum ferritin levels have high specificity for iron deficiency, high serum ferritin levels are not necessarily reflecting positive iron balance or increased iron stores. Ferritin is an acute-phase reactant and increases in the setting of inflammation, infection, malignancy, hyperthyroidism, liver disease, vitamin C

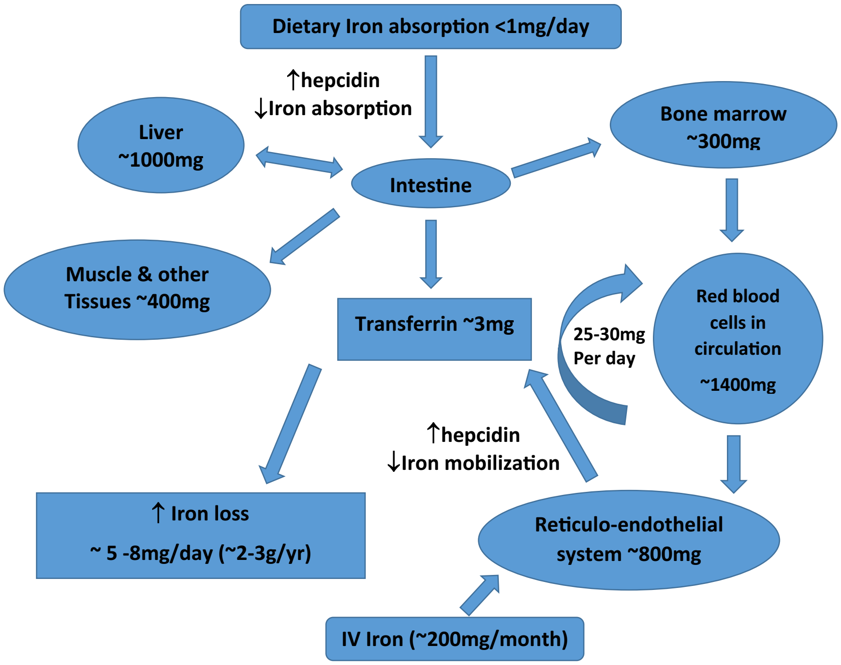
Dietary Iron absorption <1mg/day
↑hepcidin
↓Iron absorption
Liver ~1000mg
Intestine
Bone marrow ~300mg
Muscle & other Tissues ~400mg
Transferrin ~3mg
25-30mg Per day
Red blood cells in circulation ~1400mg
↑hepcidin
↓Iron mobilization
↑ Iron loss ~ 5 -8mg/day (~2-3g/yr)
Reticulo-endothelial system ~800mg
IV Iron (~200mg/month)

FIGURE 38.3 Iron homeostasis in CKD subject (hemodialysis). Values in figure are estimations and may vary between subjects. *CKD*, Chronic kidney disease.

status, and heavy alcohol intake [20]. Study in HD subjects showed that TSAT and serum ferritin correlated poorly with magnetic resonance imaging (MRI)-assessed liver iron content and are poor indicators of body iron stores [21]. Thus it should not be used alone to assess iron status or guide iron therapy [22].

Percentage of hypochromic red blood cells and the reticulocyte hemoglobin content

Both percentage of hypochromic red blood cells (% HRCs) and hemoglobin content (CHr) estimate the Hb content of red blood cells (RBCs) and not the amount of stored iron. They are more sensitive indicators of functional iron deficiency and possibly better than serum iron, TSAT, and serum ferritin in predicting response to iron administration. A metaanalysis performed for the 2016 National Institute for Health and Care Excellence guidelines demonstrated that % HRC > 6% was the most cost-effective strategy (least cost and most quality-adjusted life years) and has high specificity (95%) in predicting patients who would respond to iron. Its specificity is similar to using TSAT < 20% and ferritin <100 ng/mL (98%). The negative predictive value was better with % HRC compared with TSAT and ferritin [23]. However, the studies comprising the metaanalysis are limited, and comparisons with TSAT <20% and ferritin >100 ng/mL are lacking. Furthermore, % HRC has to be tested within 6 hours of blood collection and CHr is time sensitive to the maturation of erythrocytes and cannot be used in subjects with thalassemia [24]. Thus more evaluations of these two parameters are required before they can be applied for routine clinical use.

Hepcidin

Hepcidin is a negative regulator of iron availability and hypoferric-inducing hormone that increases with inflammation but is not a useful marker to assess iron stores. Although hepcidin has been shown to correlate with serum ferritin levels in some CKD patients [25], there were no consistent relationships observed between serum hepcidin and iron responsiveness in CKD or dialysis patients [26,27].

Iron deficiency

Iron deficiency may occur in the setting of decreased, normal, or increased total body iron. The definition of iron deficiency may fall into two categories: absolute or functional. CKD patients with reduced total body iron stores have absolute iron deficiency if left untreated. Functional iron deficiency occurs in the setting of normal or increased total body iron stores but iron delivery to the bone marrow was inadequate due to impaired iron mobilization from the reticuloendothelial system (RES) and/or increased bone marrow iron demand due to ESA treatment. Among patients with functional iron deficiency, iron sequestration in the RES occurs in the setting of inflammation of which patients have high ferritin levels but low TSAT (transferrin as a negative acute-phase protein) and erythropoiesis was restricted due to high hepcidin levels and reduced iron availability.

By convention, a serum ferritin level ≤100 μg/L (100 ng/mL) in CKD and peritoneal dialysis, and a serum ferritin ≤200 ng/mL with a TSAT ≤20% in HD is usually used as the cut-off to define absolute iron deficiency, although a TSAT of >20% does not exclude iron deficiency [15]. Functional iron deficiency or anemia of chronic disease is characterized by TSAT ≤ 20% and elevated ferritin levels ≥800 ng/mL. Patients with ESA-induced functional iron deficiency may respond to IV iron, in association with a concomitant increase in ESA dose with a decrease in ferritin levels.

Associations between iron deficiency and clinical outcomes

Absolute iron deficiency was associated with a modest increase in 1- and 2-year cardiovascular hospitalization risk but not with mortality or dialysis initiation risk, as shown in recent observational analysis [2]. Functional iron deficiency was also associated with a modest increased risk of all-cause mortality and cardiovascular hospitalization while serum ferritin level >500 ng/mL was associated with an increased risk of mortality [2]. Similarly, another retrospective analysis based on the US Veterans Data showed increased mortality with abnormal iron status in both diabetic and nondiabetic predialysis CKD subjects. Both high and low iron levels were associated with increased risk of mortality but the mortality risk was the highest among subjects with functional iron deficiency. However, it is important to take note that the study stratified iron groups based on joint quartiles of TSAT and ferritin and not using conventional clinical thresholds to define iron status [28].

Iron management in CKD

KDIGO 2012 guideline suggested iron prescription should balance the potential benefits of avoiding or minimizing blood transfusions, ESA therapy, and anemia-related symptoms against the risks of harm in individual patients (not graded). A trial of IV iron (for dialysis patients with anemia not on iron or ESA therapy) or alternatively a 1- to 3-month trial of oral iron therapy (for nondialysis CKD patients) is suggested if an increase in Hb concentration without starting ESA treatment is desired, and TSAT ≤ 30% and serum ferritin level ≤500 ng/mL (≤500 mg/L) (2C). KDIGO guideline also suggested that for nondialysis CKD patients who require iron supplementation, route of iron administration should be selected based on the severity of iron deficiency, availability of venous access, response and side effects to previous oral iron therapy, patients compliance, and cost (not graded) [18].

On the other hand, the European Renal Best Practice (ERBP) guideline suggested a trial of iron therapy either IV or oral as a first step in nondialysis CKD patients, especially in CKD 2–3, or in PD patients with anemia if absolute iron deficiency (defined as TSAT < 20% and serum ferritin <100 ng/mL) or an increase in Hb without starting ESA treatment is desired (with TSAT < 25% and serum ferritin <200 ng/mL in nondialysis CKD patients, and with TSAT < 25% and serum ferritin <300 ng/mL in dialysis patients). Following iron treatment, TSAT should not intentionally exceed 30% and serum ferritin should not exceed 500 ng/mL in both CKD and dialysis patients. For adult CKD patients on ESA therapy who are not receiving iron, a trial of IV iron is suggested if an increase in Hb or a decrease in ESA dose is desired and TSAT < 30% and ferritin <300 ng/mL. In nondialysis CKD patients, oral iron should be started as a first step if tolerated. In HD patients a course of IV iron may be considered in those having higher serum ferritin levels in the presence of hyporesponsiveness to ESA or a risk/benefit ratio going against ESA use. Caution is suggested not to exceed a ferritin value of 500 ng/mL during combined iron and ESA treatment in dialysis patients, especially in those patients with adequate TSAT > 30%.

Many HD patients with TSAT of 20%–30% and serum ferritin 200–500 ng/mL respond to iron supplementation with increase in Hb and/or reduction in ESA dosage. In the recent PIVOTAL trial, over a median of 2.1 years follow-up, HD patients randomized to high-dose proactive IV iron showed a 15% lower risk [95% confidence intervals (CI), 0.73–1.00] of primary composite endpoint event (which included nonfatal myocardial infarction, nonfatal stroke, hospitalization for heart failure, or death), as compared with the low-dose reactive IV iron group ($P < .001$ for noninferiority; $P = .04$ for superiority). In an analysis that used a recurrent-events approach, the finding remained consistent in that high-dose group was superior to low-dose group (hazard ratio, 0.77; 95% CI, 0.66–0.92). The infection rate as secondary endpoint was the same in both groups. According to the protocol, subjects randomized to the high-dose proactive group received IV iron 400 mg monthly, unless ferritin >700 μg/L or a TSAT ≥ 40%. Subjects randomized to low-dose reactive group received 0- to 400-mg IV iron monthly, with a ferritin <200 μg/L or a TSAT < 20% being a trigger for iron administration. In the trial, patients in the high-dose group received a median monthly iron dose of 264 mg [interquartile range (IQR), 200–336], as compared with 145 mg (IQR, 100–190) in the low-dose group. The median monthly ESA dose was 29,757 IU in the high-dose group and 38,805 IU in the low-dose group (median difference, −7539 IU; 95% CI, −9485 to −5582). The trial demonstrated that high-dose IV iron administered proactively was superior to a low-dose regimen administered reactively in lowering primary composite of nonfatal myocardial infarction, hospitalizations for heart failure, nonfatal stroke, and death events and resulted in lower doses of ESA administered. Furthermore, high-dose IV iron administered proactively appeared to protect against recurrent events and had fewer blood transfusions [29]. These quality data suggested that high-dose IV iron should be used more proactively in dialysis patients to reduce the dose of ESA or even prior to starting treatment with an ESA and raise the need to redefine the thresholds to initiate iron therapy in the dialysis population.

Oral and IV iron

Oral iron is cheaper but has more gastrointestinal side effects especially constipation and also lower bioavailability. However, it should still be the first-line therapy in nondialysis CKD and peritoneal dialysis patients. Table 38.2 outlined the different oral iron formulations used to correct iron-deficiency anemia in CKD. Each contains different amount of elemental iron. Absorption of ferrous iron preparations is usually 10%–15% while that of ferric iron preparations may be three to four times lower because ferric iron is poorly soluble in the alkaline environment of the gut. IV iron is given in larger doses, has better efficacy and generally better tolerated than oral iron with less gastrointestinal side effects. Table 38.3 summarized the various IV iron formulations. A systematic review, including 28 randomized studies and quasirandomized studies comparing IV versus oral iron, showed that CKD patients treated with IV iron had greater increase in Hb, serum ferritin, and TSAT than oral iron. Dialysis patients receiving IV iron showed significant reduction in ESA dose. However, there were more hypotensive and allergic reactions with IV iron [30]. Another recent updated systematic review of randomized controlled trials (RCTs) showed similar findings in CKD stages 3–5 and

TABLE 38.2 Oral iron formulations.

Oral formulations	Salt content per tablet (mg)	Elemental iron per tablet (mg)	Recommended elemental calcium dose
Ferrous sulfate (generic)	325	65	200 mg/d
Ferrous gluconate	37.5	37.5	200 mg/d
Ferric citrate	1000	210	630 mg/d
Ferric citrate hydrate	250	45	90 mg thrice-daily
Ferric fumarate	325	106	200 mg/d
Ferric maltol	30	30	30 mg twice-daily
Liposomal iron	30	30	30 mg/d
Heme iron polypeptide	12	12	36–48 mg/d

TABLE 38.3 Intravenous iron formulations.

Intravenous formulation	Test dose	Molecular weight (Da)	Iron concentration (mg/mL)	Maximum daily dose
Iron dextran	Yes	265,000	50	100 mg
Low-molecular-weight iron dextran	Yes	165,000	50	100 mg
Iron sucrose	No	34,000–60,000	20	CKD: 200 mgHD: 100 mgPD: 300–400 mg
Sodium ferric gluconate complex in sucrose	No	289,000–444,000	12.5	125 mg
Ferumoxytol	No	750,000	30	510 mg
Ferric carboxymaltose	No	150,000	50	750 mg if body weight $>$50 kg15 mg/kg if body weight $<$50 kg
Iron isomaltoside	No	150,000	100	20 mg/kg

CKD, Chronic kidney disease; *HD*, hemodialysis; *PD*, peritoneal dialysis.

5D patients that IV iron was more effective and more likely to have Hb increase >1 g/dL. Safety analysis showed similar mortality rates, serious and any adverse effect rates with oral or IV iron. IV iron was associated with fewer gastrointestinal adverse effects but higher risk of hypotension. IV iron preparations examined in the randomized trials included iron sucrose, ferric carboxymaltose (FMC), ferrumoxytol, iron dextran, ferric citrate, and ferric gluconate [31]. These data support increased use of IV iron in patients with CKD 3–5D. However, the follow-up study was limited to 3 months and there was significant heterogeneity between trials.

Potential risks of iron

Hypersensitivity

Different iron preparations may differ in their adverse effects. Some older formulations such as iron dextran have higher risk of life-threatening hypersensitivity or anaphylactic reactions and there is a strong consensus from the KDIGO 2012 Controversies Conference Report not to use these kinds of formulations. Newer iron formulations, for example, lower molecular weight iron dextran, FCM, iron isomaltoside 1000, and ferumoxytol that have much lower hypersensitivity reaction risk and doses can be infused more rapidly within 15–60 minutes would be preferred in nondialysis CKD and dialysis patients. These formulations may be superior to oral iron supplementation in enabling more cost-effective iron and anemia management in nondialysis CKD and dialysis population. Minor infusion reactions are common with IV iron infusion and may include symptoms of flushing, light-headedness, dizziness or mild chest discomfort, nauseas, or itching. Sometimes asymptomatic hypotension may develop and some patients may develop myalgia or arthralgia. These symptoms are usually self-limiting and do not require treatment. These mild infusion reactions usually resolve when infusion is stopped or infusion rate is slowed down and generally do not preclude further IV iron administration.

Iron overload

Iron overload represents a condition with increased total body iron stores that may result in body organ dysfunction. There is currently no unified definition of iron overload and how to assess iron overload in CKD patients. Serum ferritin, when elevated, may not always reflect increased total body iron stores and does not correlate with liver iron content, as it may increase as an acute-phase reactant. However, a high TSAT level together with a high serum ferritin level may be a concern for iron overload, as shown in transfusion-related iron overload and hereditary hemochromatosis.

CKD patients frequently had increased serum ferritin as a result of upregulation with inflammation. In the general population, high serum ferritin was associated with an increased risk of myocardial infarction and carotid plaque. In an observational study of 58,058 HD patients, high serum ferritin >800 ng/mL was associated with an increased mortality, but this association was markedly attenuated with adjustment for malnutrition and inflammation [32], suggesting that hyperferritinemia may relate to inflammation. Another analysis from the US, Japan, and European Dialysis Outcomes and Practice Patterns Study (DOPPS) showed similar findings that high ferritin levels were associated with elevated mortality risk but the association was attenuated more by adjustment for malnutrition and inflammation than by IV iron and ESA dose [33]. On the other hand, another observational study based on Japanese HD patients participated in the DOPPS III (2005–08) or DOPPS IV (2009–12) showed that serum ferritin level was associated with cardiovascular hospitalization regardless of inflammatory conditions. However, a U-shaped association was observed between serum ferritin and all-cause mortality in the group with low CRP levels and no association was observed in the high CRP group [34]. These data suggest limitation of using serum ferritin alone as a marker reflecting excess iron stores.

MRI provides a reliable estimate of tissue iron content in non-CKD populations [35]. Study in HD patients receiving ESA and IV iron treatment showed that most had increased liver iron content [36]. However, most peritoneal dialysis patients had normal liver iron content by MRI [37]. The clinical value of MRI in diagnosing iron overload and guiding iron therapy in CKD and dialysis patients need further evaluation.

Infections

Iron plays an important role in bacterial multiplication and phagocytic function. In vitro studies showed the association between iron availability and bacterial virulence. However, clinical studies examining associations between iron stores, IV iron dosing, and bacteremic or infection risk have produced variable results [24,38,39]. Among the nine observational studies that evaluated associations between serum ferritin and infection risk, there was generally a 1.5- to 3.1-fold higher risk of bacterial infection or infection-related mortality. This translated to an excess of 16–50 bacterial infections per 100 patient-years among those with higher serum ferritin. On the other hand, several studies did not observe any relations between serum ferritin and infection risk.

The way of IV iron administration has long been regarded to impact infection rates. A large US dialysis provider examined the iron dosing patterns of 117,050 HD patients during repeated 1-month exposure on risks of mortality and infection-related hospitalizations in the subsequent 3 months. Results showed that patients receiving bolus iron were at increased risk of infection-related hospitalization compared to maintenance iron. Risks were the highest among patients with a catheter and a recent infection. Bolus dosing was also associated with an increased risk of infection-related mortality. However, maintenance dosing did not increase risks of adverse outcomes [40]. Another retrospective analysis based on a large US dialysis provider showed that among end-stage kidney disease patients aged ≥65 years who started and survived first 90 days of in-center HD, those receiving more intensive iron treatment at moderate-to-high iron indices levels were associated with higher risks of mortality and infection-related events than those receiving less intensive iron strategies [41]. The KDIGO 2012 Clinical Practice Guideline suggested to avoid IV iron in patients with active systemic infections. At the time, the statement was ungraded due to lack of high-quality evidence [15]. The recent PIVOTAL RCT did not show any difference in adverse events in terms of the rates of hospitalizations due to infections and rates of all episodes of infections between high- and low-dose IV iron sucrose in HD patients [29]. A prespecified secondary analysis of PIVOTAL trial confirmed no difference in any infection, hospitalization for infection, and death from infection rates, confirming safety with higher dose IV iron administration in dialysis patients [42]. Similarly, another randomized trial did not observe any difference in infection rates between subjects receiving IV FMC and oral iron over 56 weeks [25]. The more recent studies provide safety reassurance of using higher doses of IV iron in the dialysis population.

Oxidative stress

Early studies raised the biological plausibility that IV iron may increase oxidative stress to peripheral leukocytes [43], promote protein oxidation [44] and lipid peroxidation [45], and thus promote atherosclerosis [46]. Iron sucrose aggravated early atherosclerosis by increasing monocyte adhesion to endothelium and promoting endothelial dysfunction in a remnant kidney model [47]. However, another animal model of accelerated atherosclerosis did not observe similar findings [48]. Although observational data suggested iron doses more than 400 mg/month may increase cardiovascular death rates [32], the prospective randomized PIVOTAL trial showed that proactive IV iron significantly reduces the risk of nonfatal myocardial infarction, nonfatal stroke, and hospitalizations for heart failure and mortality in dialysis patients compared to low-dose IV iron and did not increase cardiovascular risk [29]. This reaffirms cardiovascular safety of higher doses of IV iron in dialysis patients.

Effects on iron on CKD—mineral bone disease

Certain IV iron preparations, for example, FMC and ferric citrate, may alter CKD—mineral bone disease (MBD) parameters. For example, study showed that short-term use of ferric citrate may be associated with reduced FGF-23, serum phosphate, and urine phosphate excretion in CKD [49]. Further analysis showed that ferric citrate reduced FGF-23 partly via its effect on serum phosphate and iron balance and did not reduce serum phosphate among subjects with normal serum phosphate [50]. FMC, but not ferumoxytol, also induced circulating biologically active FGF23, renal phosphate wasting, and hypophosphatemia; decreased serum calcitriol and calcium; and increased intact parathyroid hormone (iPTH) concentrations in subjects with iron-deficiency anemia and normal kidney function [51]. Another prospective multicenter double-blind RCT in the US compared a single course of IV FMC versus ferumoxytol in adults with iron-deficiency anemia and normal kidney function over a 5-week period. The trial confirmed that FMC but not ferumoxytol rapidly increased biologically active FGF23 with renal phosphate wasting, calcitriol deficiency, and secondary hyperparathyroidism that frequently culminates in hypophosphatemia [52]. These data suggest the need to monitor for hypophosphatemia with IV iron administration, especially ferric citrate and FMC that cause hypophosphatemia.

Management of renal anemia

Erythropoietin-stimulating agents

In 1989 the US Food and Drug Administration (FDA) approved the use of recombinant EPO for renal anemia and in the last 20 years, this class of drug has revolutionized anemia management in CKD. However, these agents are not without side effects in that they may cause hypertension. More importantly, several previous RCTs raised safety concerns with these agents, resulting in several black box warnings from FDA. These trials showed that raising hematocrit to normal levels (target of 42%) or raising Hb to normal levels (13.5 g/dL) increased the risk of death or first nonfatal myocardial infarction [53], or risk of composite death and cardiovascular events [54]. Another RCT reported similar findings that correction of anemia to 13 g/dL with darbepoetin alfa may increase risk of stroke in diabetic CKD patients [55]. Additionally, there is data to suggest that a poor initial hematopoietic response to darbepoetin alfa was associated with an increased risk of death or cardiovascular events, as doses were escalated to meet the target Hb level [56]. The exact explanation for the increased adverse cardiovascular outcomes with correction of anemia is currently unclear but may relate to the doses of EPO administered and the clinical conditions that cause EPO hyporesponsiveness. Furthermore, safety concerns were raised that high-dose ESA treatment may promote angiogenesis and tumor growth and increased adverse events and outcomes [57].

A nationwide registry-based cohort study in Japan comparing the mortality risk associated with short-acting versus long-acting ESA in 194,698 HD patients showed that long-acting darbepoetin alfa and methoxy polyethylene glycol-epoetin beta were associated with a 20% higher mortality risk than short-acting ESAs such as epoetin alfa, beta, and kappa. The association was attenuated but remained significant after adjusting for demographics, clinical factors, facility indicators, and, when considered, a propensity score-matched cohort. Notably, the difference in risk was higher among those receiving higher ESA doses and those with a high erythropoietin resistance index. Furthermore, the use of long-acting ESA was associated with an increased rate of death from cardiovascular disease, infections, and malignancies [58]. However, the study was retrospective and data were not generalizable to populations other than the Japanese. As the US FDA and the European Medicines Agency required confirmation of cardiovascular safety of ESA particularly when aiming for higher Hb levels, a large randomized postapproval noninferiority trial was performed in 2818 dialysis and nondialysis CKD patients to compare all-cause mortality and cardiovascular events of methoxy polyethylene glycol-epoetin beta versus other ESAs. The results showed that methoxy polyethylene glycol-epoetin beta was not associated with increased risk of all-cause mortality and major adverse cardiovascular events (MACE) compared to other ESAs [59].

Recent randomized trial examined whether targeting Hb level of 11−13 g/dL using darbepoetin alfa may affect kidney outcomes compared to a lower Hb target of 9−11 g/dL in nondiabetic advanced CKD subjects in Japan. The eGFR of study subjects ranged between 8 and 20 mL/min/1.73 m^2. The primary study outcome was a kidney composite endpoint (starting maintenance dialysis, kidney transplantation, eGFR ≤ 6 mL/min/1.73 m^2, and 50% reduction in eGFR). The results showed that the kidney composite endpoint and cardiovascular events did not differ between the high- and low-Hb groups during a mean study period of 73.5 ± 29.7 weeks [60].

HIF propyl hydroxylase domain inhibitors

With the discovery of a major transcription factor HIF for the EPO gene in 1992, drugs that inhibit the HIF PHD were developed. This class of drugs called HIF stabilizers or PHD inhibitors prevents the proteasomal degradation of HIF-α, thus induces the EPO gene. During hypoxia, PHDs are less active and HIF-α can bind to HIF-β subunit, translocate into the nucleus, and induce a physiological response to hypoxia. It induces the EPO gene and stimulates erythropoiesis, increases intestinal absorption of iron and mobilization of iron, and coordinates other cellular responses, including angiogenesis, lipid and glucose metabolism, mitochondrial function, cell growth and survival, vasodilatation, cell migration, and inflammation (Fig. 38.1).

PHD inhibitors mimic the response with hypoxia, stabilize HIF-α, and are oral drugs. They stimulate endogenic EPO production from native kidneys or the liver. PHD inhibitors also change iron metabolism. They markedly reduce hepcidin and effectively maintain Hb levels with less iron need and correct anemia in inflamed CKD patients with functional iron deficiency. They also reduce ferritin and increase total iron-binding capacity in CKD [61]. There are currently five PHD inhibitors, roxadustat, daprodustat, vadadustat, molidustat, and enarodustat and phase III trials with these PHD inhibitors are currently in progress in different parts of the world. Phase II trials of all these drugs with various follow-up durations showed a dose-dependent improvement in erythropoiesis and anemia.

In a multicenter open-label phase IIb study conducted in anemic nondialysis CKD patients, 92% achieved the required Hb response (i.e., Hb ≥ 1 g/dL from baseline and Hb ≥ 11 g/dL) after 16 weeks roxadustat (FG-4592 or ASP1517) treatment. Hepcidin levels decreased by 16.9%. Roxadustat-induced Hb increases were independent of C-reactive protein levels and iron repletion status. Furthermore, there was a reduction in total cholesterol level and no serious drug-related adverse events [61].

A multicenter randomized open-label active-controlled phase III trial has recently confirmed safety and efficacy of oral roxadustat in dialysis patients of which nearly 90% were HD and 10% were peritoneal dialysis. The study recruited 304 dialysis patients receiving ESA therapy for at least 6 weeks and patients were randomized in a 2:1 ratio to receive either oral roxadustat or subcutaneous epoetin alfa three times a week for 26 weeks with the primary endpoint being the mean change in Hb level from baseline to an average level during weeks 23−27. The results showed that oral roxadustat was noninferior to parenteral epoetin alfa in increasing Hb level. Furthermore, oral roxadustat was associated with a greater increase in iron and TSAT than parenteral epoetin. Furthermore, roxadustat was associated with significantly greater reduction in serum hepcidin levels, total cholesterol and LDL-cholesterol levels. However, hyperkalemia and upper respiratory tract infection occurred at a higher frequency with roxadustat than epoetin alfa while hypertension occurred at higher frequency with epoetin alfa [62]. In another phase III trial conducted at 29 sites in China, 154 nondialysis CKD patients with Hb between 7.0 and 10.0 g/dL were randomized to receive roxadustat or placebo three times a week for 8 weeks in a double-blind fashion followed by an 18-week open-label period during which all patients received roxadustat and parenteral iron was withheld. In the primary analysis, roxadustat group had greater increase in Hb levels than placebo. Roxadustat group showed more reduction in serum hepcidin and total cholesterol levels than placebo group. Hyperkalemia and metabolic acidosis occurred more frequently in roxadustat than placebo group. The efficacy of roxadustat in correcting Hb was maintained throughout the 18-week open-label period [63].

A recent systematic review, including 6 RCTs that comprised 1001 patients of which 70.6% were treated with roxadustat and 294 controls and with a median follow-up of 8 weeks, concluded that roxadustat increases Hb, serum transferrin, intestinal iron absorption, and reduces hepcidin in both dialysis and nondialysis CKD patients [64]. In a pooled efficacy and cardiovascular safety analysis by Provenzano et al., roxadustat was superior to epoetin alfa in anemia correction and maintenance of Hb, and comparable to epoetin alfa in its cardiovascular safety profile. Event risk for MACE and mortality was similar for nondialysis CKD and prevalent dialysis patients randomized to roxadustat or placebo/epoetin alfa. In incident dialysis patients, roxadustat was associated with a reduced risk of first MACE, heart failure, and unstable angina requiring hospitalization than epoetin alfa [65].

Similarly, a 4-week phase IIa trial and a 24-week open-label trial with daprodustat (GSK1278863) showed that daprodustat effectively increased and maintained Hb during the study period [66,67]. A 6-week phase IIa trial and a 20-week phase IIb trial with vadadustat (AKB-6548) have reported similar findings of a dose-dependent increase in Hb in nondialysis CKD patients [68,69]. Molidustat (BAY 85-3934), a novel selective oral HIF PHD inhibitor, has also been evaluated in three 16-week, phase IIb studies in anemic nondialysis CKD patients [DaIly orAL treatment increasing endOGenoUs Erythropoietin (DIALOGUE) 1 and 2] and in dialysis patients (DIALOGUE 4). Molidustat was generally well tolerated and associated with estimated mean Hb levels increase of 1.4−2.0 g/dL [70]. Recent extension study of DIALOGUE showed that molidustat was well tolerated up to 36 months and was a comparable alternative to darbepoetin and epoetin alfa as a treatment for anemia in CKD [71]. These data form an important basis for further phase III trials of the different PHD inhibitors.

Potential adverse effects of PHD inhibitors

PHD inhibitors have diverse physiological actions beyond stimulation of endogenous EPO production. The activation of HIF and the increase in VEGF are worrisome for possible risks of promoting angiogenesis, tumor growth, or diabetic retinopathy [72]. HIF activation may also cause new onset or exacerbate pulmonary hypertension [73]. Thus further RCTs are required to evaluate the long-term safety profile of this class of novel therapeutic drugs for anemia.

Initiation and maintenance treatment with ESA

Initiation of ESA therapy

According to KDIGO 2012 guideline, all correctable causes of anemia, including iron deficiency, B12, folate deficiency, and inflammatory states, should be addressed before initiation of ESA. In initiating and maintaining ESA therapy, KDIGO recommended the potential benefits of reducing blood transfusions and anemia-related symptoms should be balanced against the risks of harm in individual patients (e.g., stroke, vascular access loss, and hypertension) (1B). KDIGO recommended great caution with ESA therapy in CKD patients, if at all, with active malignancy, in particular when cure is the anticipated outcome (1B), a history of stroke (1B) or a history of malignancy (2C) [22]. The ERBP felt that these issues should take into account when weighing the risk/benefit ratio of prescribing ESA therapy. However, they are not absolute contraindications to ESA treatment and nephrologists should discuss them with each patient, balancing the risk versus benefit [74].

For adult nondialysis CKD patients with Hb < 10.0 g/dL, KDIGO suggested the decision whether to initiate ESA therapy be individualized based on the rate of fall of Hb level, prior response to iron therapy, the risk of blood transfusion, the risks related to ESA therapy and the presence of symptoms attributable to anemia (2C). KDIGO suggested ESA therapy should not be initiated in CKD patients with Hb ≥ 10 g/dL.

The ERBP suggested to individualize initiation of ESA therapy in nondialysis (ND)-CKD and not to allow Hb to fall <10 g/dL in ND-CKD patients. Furthermore, ESA therapy should not be initiated if there is a temporary and obvious potential reversible cause of anemia identified such as iron deficiency, bleeding, infections, or inflammations. ERBP also stratified management for low- and high-risk patients. For high-risk patients, including those with asymptomatic ischemic heart disease, ESA should be initiated at Hb between 9 and 10 g/dL to maintain Hb level of >10 g/dL. In low-risk patients or those in whom a clear benefit on quality of life can be foreseen, ESA could be initiated at higher Hb levels (but not >12 g/dL) [74].

For adult dialysis patients, KDIGO suggested ESA therapy should be used to avoid having Hb level fall below 9.0 g/dL by starting ESA therapy when Hb is between 9 and 10 g/dL (2B). It is not entirely certain why slightly different threshold was applied in the initiation of ESA therapy for nondialysis and dialysis CKD patients by KDIGO. However, KDIGO suggested that individualization of ESA therapy is reasonable and ESA may start above 10 g/dL if some patients may have improvement in quality of life at higher Hb levels (ungraded) [22]. Similarly, ERBP suggested to individualize ESA therapy in dialysis CKD patients. Hb should not fall <10 g/dL in CKD 5D patients. In low-risk patients, in those with ischemic heart disease and worsening ischemic symptoms associated with anemia, or in those in whom a clear benefit on quality of life can be foreseen, ESA therapy could be initiated at higher Hb level but not exceed 12 g/dL. In high-risk patients, ESA therapy could be initiated at Hb between 9 and 10 g/dL to maintain a target Hb level of 10 g/dL

[74]. We summarize the various clinical practice guidelines on the Hb thresholds and targets in initiation and maintenance of ESA therapy, respectively in Table 38.4.

Maintenance of ESA therapy

KDIGO 2012 suggested that ESA therapy should not maintain Hb above 11.5 g/dL in adult CKD (2C) and not above 13 g/dL in all adults (1A). Individualization of therapy will be necessary as some patients may have improvements in quality of life at Hb level >11.5 g/dL and will be prepared to accept the risks (not graded). Furthermore, decreasing ESA dose is preferred to withholding ESA when a downward adjustment of Hb concentration is needed (2C) [22]. ERBP suggested ESA therapy should generally maintain Hb levels between 10 and 12 g/dL in CKD patients but should individualize the value within this target range according to comorbidities of patients. Caution should be used in patients with specific risk factors especially among diabetics with vascular disease, cancer, or in those who are hyporesponsive to ESA treatment, and in these patients, it is better to aim toward the lower Hb levels within the range between 10 and 12 g/dL. ERBP also made a similar statement as KDIGO that Hb should not intentionally aim >13 g/dL during ESA therapy [74].

The rationale for being cautious of a higher Hb target and setting a lower Hb target in the maintenance phase of ESA therapy by the different guideline bodies was based on the results of several large clinical trials showing that complete anemia correction has no benefit but may incur an increased risk of death and cardiovascular events.

ESA hyporesponsiveness

Approximately 5%–10% of patients with CKD demonstrated hyporesponsiveness to ESA [75]. Conventionally, this is defined as a continued need for greater than 300 IU/kg/week EPO or 1.5 mg/kg/week darbepoetin administered by subcutaneous route. CKD patients with ESA hyporesponsiveness were noted to have a worse clinical outcome, greater risk of mortality, and more progression to ESRD [76]. KDIGO 2012 classified patients as having ESA hyporesponsiveness if they have no increase in Hb level from baseline after

TABLE 38.4 Clinical practice guidelines on initiation and maintenance of erythropoietin-stimulating agent (ESA) therapy in chronic kidney disease.

	KDIGO 2012	ERBP 2012
Initiation of ESA therapy	Individualize ESA initiation based on rate of fall in Hb, prior response to iron, risk of blood transfusion, risk related to ESA therapy, and presence of symptoms attributable to anemia	
• Nondialysis CKD	Initiate ESA therapy if Hb < 10 g/dL (2C) Do not initiate ESA if Hb ≥ 10 g/dL (2D)	Hb should not fall <10 g/dL Low-risk patients—can consider starting ESA at higher Hb (but not >12 g/dL) High-risk patients—start ESA at Hb between 9 and 10 g/dL Patients with ischemic symptoms—ESA could start at higher Hb (>10 g/dL)
• Dialysis CKD	Initiate ESA when Hb between 9 and 10 g/dL Avoid Hb fall <9 g/dL (2B)	Avoid Hb fall <10 g/dL Low-risk patient—ESA could start at higher Hb but not exceed 12 g/dL High-risk patient—start ESA at Hb between 9 and 10 g/dL
Maintenance of ESA therapy	ESAs not be used intentionally to increase Hb >13 g/dL in all CKD (1A)	
• Nondialysis CKD	Hb with ESA treatment should not be >11.5 g/dL (2C) Individualize therapy as some patients may have improvements in quality of life at Hb >11.5 g/dL and prepare to accept the risks (ungraded)	Low-risk patient—maintain Hb between 11 and 12 g/dL High-risk patient—maintain Hb ∼10 g/dL
• Dialysis CKD	Hb with ESA treatment should not >11.5 g/dL (2C) Individualize therapy as some patients may have improvements in quality of life at Hb >11.5 g/dL and prepare to accept the risks (ungraded)	Maintain Hb between 10 and 12 g/dL and individualize the value within this range according to comorbidities of patients High-risk patient—maintain Hb ∼10 g/dL or lower end within this range

CKD, Chronic kidney disease; *ERBP*, European Renal Best Practices; *ESA*, erythropoietin-stimulating agents; *Hb*, hemoglobin; *KDIGO*, Kidney Disease Improving Global Outcomes.

the first month of ESA treatment given on appropriate weight-based dosing (ungraded). In patients with ESA hyporesponsiveness, KDIGO suggested avoiding repeated escalations of ESA dose beyond double the initial weight-based dosing (2D).

There are many possible factors contributing to ESA hyporesponsiveness. These include inflammation, inadequate dialysis, hyperparathyroidism, nutrient deficiencies (vitamin B12, folate, vitamin C, carnitine), angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, aluminum overload, antibody-mediated pure red cell aplasia, primary bone marrow disorders, myelosuppressive agents, hemoglobinopathies, hemolysis, and hypersplenism. It is therefore important to look for these possible causes in case of ESA hyporesponsiveness. For the relevance of this chapter, we will discuss the nutritional factors that may contribute to ESA hyporesponsiveness. It includes deficiencies of vitamin B12, folate, vitamin C, and carnitine. We also discuss briefly the relations between vitamin D and anemia.

Contributions of various other nutrition factors relating to anemia in CKD

Carnitine

Carnitine is an amino acid derivative synthesized by the essential amino acids lysine and methionine [77]. It plays an essential role in the β-oxidation of fatty acids by catalyzing their transport into the mitochondrial matrix, modulating the ratio of cellular and mitochondrial acyl CoA to free CoA, stabilizing cell membranes by removing long-chain acyl CoAs and excess acyl groups from the body [78]. Meat, fish, and dairy products are major dietary sources of L-carnitine, which are absorbed mainly in the small intestine via an active organic cation transporter [79]. Carnitine is also synthesized endogenously from trimethyllysine in the liver and the kidneys [80] but is concentrated in the cardiac and skeletal muscles, which depends on fatty acids for energy metabolism [81]. In addition to carnitine synthesis, the kidneys play an important role in carnitine homeostasis and maintaining carnitine concentrations within a narrow homeostatic range by saturable tubular reabsorption. The kidneys also play an important role in the esterification and excretion of carnitine [78]. Dialysis patients have reduced renal synthesis of L-carnitine and increased dialytic losses of carnitine, thus increasing their risk of carnitine deficiency. Vegetarians also excreted markedly less L-carnitine than omnivores as they had 10%–20% lower plasma L-carnitine concentration [82]. One study showed that L-carnitine levels decreased significantly within the first week of HD initiation and continued to decline over the first 12 months of dialysis and could be attributed to increased dialysis clearance of carnitine [83]. The prevalence of carnitine deficiency, defined as a serum-free carnitine level $<20\ \mu mol/L$, and that of carnitine insufficiency, defined as an acyl/free carnitine ratio >0.4, was estimated to be 25.3% and 86.7%, respectively, in one cohort. Patients at high risk of carnitine deficiency accounted for 64.7% [84]. Another study reported the prevalence of carnitine deficiency to be 8.8% and carnitine insufficiency 82.3% in peritoneal dialysis patients [85].

L-Carnitine deficiency may give rise to anemia, intradialytic hypotensive symptoms, muscle weakness and fatigue, impaired exercise capacity, cardiomyopathy, hyperlipidemia, and inflammation [81]. However, treatment with L-carnitine has not been proven to be useful in ameliorating these complications associated with CKD [81].

L-Carnitine deficiency may contribute to anemia by reducing erythrocyte membrane stability and increasing osmotic fragility, thus reducing erythrocyte survival [86]. Early study showed that serum total carnitine levels were inversely correlated with erythrocyte fragility and weekly erythropoietin doses in HD patients [87]. L-Carnitine supplementation may reduce red cell deformity, improve red cell membrane stability, and increase hematocrit [88,89]. Several RCTs did not observe any significant change in Hb with IV L-carnitine in chronic HD patients [90,91]. Existing randomized trials were mostly very small sample size, short duration, and dated. The doses of IV carnitine used were also variable ranging from 2 g to 25 mg/kg [89]. A multicenter double-blind randomized study in 92 incident HD patients showed that L-carnitine 1 g, given IV after each HD session for 1 year did not improve their response to EPO [92]. Putting together available evidence, IV carnitine is not a useful adjunctive therapy for anemia in HD patients. KDIGO 2012 suggested not using L-carnitine as an adjuvant to ESA treatment. Further large RCT will need to explore the full pharmacologic potential of IV carnitine.

Ascorbic acid

Ascorbic acid increases iron absorption from foods and is the most efficient promoter of nonheme iron absorption [93]. It maintains iron in a reduced state and promotes the enzymatic incorporation of iron into protoporphyrin, an intermediate in heme biosynthesis [94,95]. In HD patients, iron metabolism may be dysregulated with diminished utilization of iron stores. Ascorbic acid improves iron availability through its role in maintaining iron in a reduced state [96].

Subclinical ascorbic acid deficiency was reported in at least 30%−50% of dialysis patients [97,98]. Several factors may contribute to ascorbic acid deficiency, including restricted dietary intake of fruits and vegetables in dialysis patients and increased loss of ascorbic acid during dialysis. Epidemiologic studies suggested that low total ascorbic acid level was associated with an increased risk of all-cause death and cardiovascular mortality in HD patients [97,99]. Early study demonstrated that IV administration of high-dose ascorbic acid 300 mg thrice-weekly in HD patients treated with epoetin and serum ferritin >500 ng/mL increased hematocrit, serum iron, and TSAT [100], suggesting that IV ascorbic acid may improve iron utilization. Subsequent to this observation, several RCTs evaluated the efficacy of IV ascorbic acid in ESA-treated dialysis patients. Results of these trials were summarized in two systematic reviews [101,102]. The systemic review by Deved et al. combined three randomized trials and showed that ascorbic acid increased Hb, decreased ESA dose, and increased TSAT [101]. The other systematic review by Einerson et al. included five studies and concluded that adjuvant ascorbic acid increased Hb and TSAT in HD patients with EPO hyporesponsiveness. The significant rise in TSAT suggested that the positive response with EPO may relate to improved iron utilization with ascorbic acid treatment [102].

The latest National Kidney Foundation (NKF) Kidney Disease Outcome Quality Initiative (KDOQI) nutrition guidelines in CKD did not suggest ascorbic acid as adjuvant therapy for anemia in CKD. However, the guideline suggested that in adults with CKD 1−5D and posttransplant who are at risk of ascorbic acid deficiency, it is reasonable to consider supplementation to meet the recommended intake of at least 90 mg/d for men and 75 mg/d for women (opinion).

A potential concern with high-dose ascorbic acid treatment is oxalate accumulation [103]. The ascorbic acid dose required to increase iron mobilization from tissue stores and improve ESA responsiveness is much higher than the daily recommended dietary allowance [104]. As ascorbic acid is converted to oxalic acid that needs kidney function for clearance [105], it may accumulate in dialysis patients. Thus KDIGO does not suggest ascorbic acid as an adjuvant treatment for anemia in dialysis patients.

Vitamin D

25-Hydroxyvitamin D deficiency and insufficiency are highly prevalent in dialysis and CKD population [106,107]. Epidemiologic studies in the general population as well in CKD have linked vitamin D deficiencies with anemia [108−110] and EPO responsiveness [111]. One potential mechanism may involve its action on the hepcidin−proinflammatory cytokines pathway [112]. Vitamin D is antiinflammatory [113]. In vitro study showed that treatment with calcitriol reduces inflammatory cytokine release, suppresses hepcidin mRNA expression, and increases ferroportin mRNA expression from monocytes, suggesting that vitamin D plays a regulatory role on the hepcidin-ferroportin axis [114,115]. By suppressing hepcidin expression and inflammation, vitamin D increases iron mobilization from tissue stores, promotes erythropoiesis, and improves anemia of inflammation [112].

Another mechanism that underlies the association between vitamin D and anemia of inflammation is through suppression of erythropoiesis. Inflammatory cytokines may suppress erythropoiesis by inhibiting the production of EPO and differentiation and proliferation of erythroid progenitor cells [116]. Vitamin D improves erythropoiesis by promoting proliferation of erythroid burst-forming units (BFU-E) and acts synergistically with EPO to increase BFU-E proliferation [117]. Adding vitamin D3 treatment to rats that received ribavirin as part of the hepatitis C treatment increased their Hb levels and increased EPO levels compared to rats that did not receive vitamin D3 [118], suggesting that vitamin D may protect against drug-induced disturbances in erythropoiesis. Vitamin D treatment also reduced ESA requirements in CKD patients [111,119].

Vitamin D and anemia are associated via other hormones in the CKD−MBD axis. Elevated PTH, a key derangement in CKD−MBD, causes osteitis fibrosa cystica and is associated with marrow fibrosis. Study showed that the degree of erythropoietin responsiveness depended both on the severity of secondary hyperparathyroidism and also the extent of marrow fibrosis [120]. Early animal study showed that iPTH inhibits erythropoiesis through reduction of erythroid progenitor formation and adequate levels of EPO can overcome this action of PTH [121]. PTH may also increase calcium influx into RBCs and affect osmotic fragility of these cells, thus reduce the survival of erythrocytes [122]. In clinical studies, elevated iPTH levels were associated with more anemia and increased odds of EPO resistance in CKD [123,124]. Uncontrolled studies showed that dialysis patients who underwent parathyroidectomy [125] or received cinacalcet treatment [126] to lower very high PTH levels had increases in Hb. This provides indirect evidence that severe secondary hyperparathyroidism contributes to anemia in CKD. Control of severe secondary hyperparathyroidism using vitamin D analogs has been shown to improve anemia and EPO responsiveness [127,128]. Treatment of secondary hyperparathyroidism may thus serve as a mechanism by which vitamin D treatment improves anemia in dialysis patients. However, it is currently unknown whether this association is independent or dependent of vitamin D. KDIGO or NKF KDOQI did not recommend vitamin D as an adjuvant treatment for anemia in dialysis or nondialysis CKD patients.

Preliminary evidence suggested that FGF-23 and Klotho may be involved in erythropoiesis. Coe et al. showed that FGF-23 knockout mice had more erythrocytosis, more BFU-E proliferation, and higher serum EPO compared to wild-type mice. Notably, fetal livers had similar hematopoietic changes, suggesting that they were not the result of altered bone marrow niche alone. On the other hand, administration of FGF-23 in wild-type mice resulted in a rapid decrease in erythropoiesis. The effects of FGF-23 on erythropoiesis appeared independent of the high vitamin D levels in these mice. These data suggest FGF-23 may be a negative regulator of erythrocyte production and differentiation and may contribute to anemia in patients with CKD [129]. In line with this animal data, study also reported a negative correlation between Hb and FGF-23 in CKD subjects [130]. A Klotho knockout mouse model, Klotho being a necessary cofactor for FGF-23, had increased erythrocytosis along with increased BFU-E in bone marrow compared to wild-type and heterozygous mice though hematopoietic stem cells in the bone marrow were reduced [131].

FGF-23 is closely associated with iron homeostasis and iron deficiency has been suggested to be a key driver of FGF-23 [132]. Early study observed FGF-23 increase with reduction in iPTH with administration of low-molecular-weight iron dextran in HD patients [133]. The link between FGF-23 and iron was further demonstrated in a 12-week double-blind randomized placebo-controlled trial with ferric citrate in stages 3–5 CKD patients with iron-deficiency anemia [49]. Ferric citrate not only improved anemia and iron stores but also reduced serum phosphate, FGF-23, and urine phosphate excretion in nondialysis CKD [49]. Study also showed that ferric citrate reduced FGF-23 and improved EPO responsiveness in HD patients [134]. Given elevated FGF-23 predicted an increased mortality and cardiovascular risk in CKD and dialysis patients [135,136], whether iron treatment by lowering of FGF-23 may improve outcomes of CKD warrant further evaluation. Table 38.5 summarized the various associations between CKD–MBD biomarkers, erythropoiesis, and iron indices.

Folic acid

Folic acid is a key nutrient required for erythropoiesis. It serves as a cofactor for DNA synthesis and its requirement increases in the face of increased RBC turnover. Folic acid is also an effective treatment to lower hyperhomocysteinemia. The exact prevalence of folic acid deficiency in dialysis patients is not known. Some reports suggested a prevalence of folic acid deficiency of 10%–12% in HD patients [137]. Dialysis patients are at risk of folic acid deficiency due to dietary restriction of green leafy vegetables for potassium concerns. Folic acid is also lost during dialysis therapy particularly with high-flux dialysis [138]. Studies suggested that folic acid deficiency may mediate ESA resistance in dialysis patients and folic acid supplementation may reduce EPO requirement [139–141]. However, there are also reports that high-dose folate supplementation did not improve EPO responsiveness [142]. Folic acid has also not been shown to improve overall survival and cardiovascular outcomes of dialysis patients [143]. While it is important to evaluate serum B12 and folate levels in the initial evaluation of anemia [22], routine folate supplementation with or without B-complex is not recommended for CKD patients with hyperhomocysteinemia. Folic acid is not considered a useful adjuvant treatment for anemia in CKD patients without folic acid deficiency [22]. NKF KDOQI suggested folate,

TABLE 38.5 Associations between chronic kidney disease-mineral bone disease parameters and erythropoiesis-related parameters.

Vitamin D	PTH	FGF-23
↓Proinflammatory cytokines	↑Marrow fibrosis	↓Erythropoietin
↓Hepcidin	↑Erythropoietin resistance	↓Erythroid cells
↑Serum iron	↓Erythropoietin	↓Proerythroblasts
↑Hemoglobin	↓Erythroid progenitor formation	↓Erythrocytosis
↑Erythropoietin	↓Erythrocytosis	↓Hemoglobin
↓Erythropoietin resistance	↓Hemoglobin	
↑Erythroid progenitor proliferation		
↑Erythrocytosis		

FGF-23, Fibroblast growth factor-23; *PTH*, parathyroid hormone.

vitamin B12, and/or B-complex supplement should be prescribed to correct folate or vitamin 12 deficiency/insufficiency in CKD 1−5D and posttransplant patients based on clinical signs and symptoms (2B).

Vitamin B12

Deficiency of vitamin B12 inhibits purine and thymidylate synthases, impairs DNA synthesis, and causes erythroblast apoptosis, resulting in anemia from ineffective erythropoiesis. Thus serum vitamin B12 level should be included in the initial evaluation of anemia in CKD. Open-label single-arm study showed that B12 supplementation in HD patients with B 12 level <300 pmol/L maintained Hb level with reduced EPO requirement [144]. However, there are no randomized studies in this regard. NKF KDOQI nutrition guidelines suggested supplementing B12 only for those CKD 1−5D and postkidney transplant with vitamin B12 deficiency/insufficiency.

Vitamin B6

Vitamin B6 is an important nutrition factor in erythropoiesis. It is a cofactor involved in the formation of aminolevulinic acid, a rate-limiting step in heme biosynthesis and it plays a role in incorporating iron into protoporphyrin, the final step in heme synthesis [145,146]. Vitamin B6 is consumed during erythropoiesis and oral B6 supplementation prevents depletion of erythrocyte B6 [146]. In dialysis patients, vitamin B6 metabolism is deranged with resulting low pyridoxal phosphate levels, a main active metabolite of vitamin B6 [147]. There is also increased vitamin B6 loss in the dialysate especially with high-flux dialysis [148]. The prevalence of B6 deficiency was estimated to be nearly 40% in dialysis patients [149,150]. However, a previous randomized trial showed that IV pyridoxine increased rather than decreased EPO resistance in HD patients [150]. There are otherwise no RCT data. Thus pyridoxine status is not included in the initial evaluation of anemia and vitamin B6 is not useful adjuvant therapy for anemia in CKD patients.

Declaration of conflict of interest

None to be declared.

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PART VI

Obesity, Metabolic Syndrome and Diabetes Mellitus

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CHAPTER

39

Metabolic syndrome and kidney disease

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Introduction

Humans have evolved over the last centuries when food was not always available, and such nutritional challenges created efficiency in storing excess calories and limiting energy expenditure. In 1962 Dr. Neel described a metabolic process whereby humans adapt to dynamics in caloric intake and named this evolutionary adaptation the thrifty genome [1]. As the body stores the excess intake of calories that exceed energy expenditure, insulin resistance ensures. While a thrifty genome was helpful with food scarcity, efficiency of caloric storage can be now viewed as maladaptive if food scarcity no longer exists and caloric intake is instead excessive. In this chapter, we review metabolic syndrome and its origins and the organ damage that often accompanies metabolic syndrome, including chronic kidney disease (CKD). In this chapter, you will learn the cellular consequences of insulin resistance and postulated mechanisms that mediate kidney disease in the setting of metabolic syndrome.

Metabolic syndrome and its origins

Metabolic syndrome is a nutritional disorder rooted in the overconsumption of calories that exceeds energy expenditure leading to overweight and obesity. Obesity, defined as a body mass index (BMI) greater than or equal to 30 kg/m^2, continues to be a growing epidemic within the United States and globally. Over 93 million United States adults are now obese but the prevalence differs by age and racial/ethnicity. Within age-groups the highest prevalence is among men (40.8%) and women (44.7%) age 40−59 years old and lowest among men (34.8%) and women (36.5%) age 20−39 years [2]. Across racial/ethnic groups, obesity prevalence ranges from as low as 10.1% and 14.8% among Asian men and women, respectively, to as high as 43.1% and 50.6% among Hispanic men and women, respectively. Across the globe, obesity affects approximately 650 million people while over 1.3 billion adults are overweight, defined as a BMI between 25 and 29.9 kg/m^2 [3]. These statistics are based on BMI and can be misleading. Metabolic syndrome can occur with increased visceral adiposity known as android obesity that itself increases cardiovascular disease (CVD) and diabetes risk. Many argue that waist circumference or waist-to-hip ratio should be used to define obesity instead of BMI because of the importance of visceral adiposity. In addition, due to racial/ethnic differences in body size, racial/ethnic-specific definitions for both BMI and waist circumference have also been suggested.

The epidemic of obesity around the globe has been fueled by a ubiquity of calorically dense, highly palatable processed foods but not everyone has been affected. Differences in obesity risk have been attributed to numerous genetic variants across the genome, but these discovered variants each contribute very small effects on energy intake or energy expenditure. Thus the overwhelming majority of obesity is considered polygenetic [4] and a complex disease meaning that obesity occurs due to the interaction of multiple genetic factors that determines susceptibility to obesity combined with an obesogenic environment (access to densely caloric foods and sedentary lifestyle). Rarely, obesity is attributed to a single genetic variant (monogenetic obesity) or to several defined genetic variants/defects or chromosomal abnormalities; these obesity

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cases are usually accompanied by developmental abnormalities and termed syndromic obesity.

Regardless of genetic background, weight gain will not occur without energy intake exceeding energy expenditure. Weight gain is essential for development of metabolic syndrome but it is not sufficient because where the excess calories are stored is just as important as the weight gain itself. In contrast to overall obesity risk that is mainly mediated by nongenetic factors, the distribution patterns of adiposity are strongly familial, and genetically determined as demonstrated by strong sex differences in adiposity distribution. In some persons the excess adipose tissue may be readily stored in hips, thighs, and buttocks (peripheral), while in others the adipose tissue is mainly stored in the abdomen, liver, and muscles (truncal). Over 80% of body fat is normally stored in the subcutaneous adipose tissues while the other 20% is stored in visceral adipose tissue (omentum, mesentery, etc.) [5]. In some individuals, excess caloric intake is stored as fat preferentially in visceral adipose tissue and this is largely determined by genetic factors. These genetic factors that influence body fat distribution also account for sex differences in body fat distribution [6]. This adipose tissue stored in the abdomen or visceral adipose tissue leading to android obesity primarily drives the development of metabolic syndrome, or the clustering of major cardiovascular risk factors, including hypertension, dyslipidemia, and glucose intolerance.

In addition to where the fat is distributed, the overall ability to store excess fat also varies across individuals. The ability to store excess calories as defined by the total number of adipose cells is also largely genetic but can be influenced during childhood via being overweight. The number of adipose cells increases during childhood but then, after adolescence, remains constant during adulthood [7]. Thus regardless of weight loss or weight gain, the total number of adipose cells generally stays the same during the adult life span of an individual. Adipose cells do demonstrate cell turnover at a rate of 10% annually, but this turnover does not differ by obesity status and does not alter the total number of adipose cells available for storage [7]. When storage capacity of existing adipocytes is exceeded, fat must then be stored in the liver and muscle. Thus metabolic syndrome can be viewed as the immersion of a genetically susceptible individual combined with excess caloric intake.

Metabolic syndrome and its definition

In 1988 the presence of several metabolic traits was noted to associate with a heightened risk of type 2 diabetes and CVD. This clustering of elevated glucose levels, hyperinsulinemia, high levels of very-low-density lipoprotein triglycerides, and low-high-density lipoprotein cholesterol was entitled Syndrome X by Dr. Reaven [8] and then later changed to Metabolic Syndrome [9,10]. Increased waist circumference was later added as an additional metabolic syndrome trait by Norman Kaplan [11]. The Third Report of the Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III, or ATP III) from the National Cholesterol Education Program (NCEP) later established a definition for metabolic syndrome. The presence of at least three of the following five criteria defined metabolic syndrome: central obesity (waist circumference in men >102 cm and in women >88 cm), hypertriglyceridemia (≥150 mg/dL), low-high-density lipoprotein (HDL) cholesterol (men <40 mg/dL, women, <50 mg/dL), elevated fasting glucose (≥110 mg/dL), and elevated blood pressure (BP) (≥130/85 mmHg) (see Table 39.1) [12]. The World Health Organization (WHO) also developed a definition of metabolic syndrome that tied factors associated with insulin resistance such as obesity, dyslipidemia, and hypertension. The WHO definition also allowed persons with diabetes to be diagnosed with metabolic syndrome but the diagnostic criteria could not be readily applied in clinical settings. The European Group for Study of Insulin Resistance postulated that insulin resistance was central to metabolic syndrome and used elevated fasting insulin (<75th percentile) to define insulin resistance but this meant persons with diabetes could not be diagnosed. The European group also eliminated increased urine albumin excretion as a metabolic syndrome trait given its lack of specificity with insulin resistance [13].

The use of hyperinsulinemia to define metabolic syndrome is troublesome because of heterogeneity in measurement, differing classification schemes, and lack of standardization across studies [9]. Many studies define hyperinsulinemia as insulin levels greater than the 75th percentile for the general population but this particular definition can be misleading because this assumes a threshold dependence for insulin resistance. Similar to BP, it is likely that insulin resistance is a continuous measure where even low levels of insulin resistance can lead to endothelial dysfunction and organ dysfunction in susceptible individuals. In addition, levels of insulin that indicate resistance likely vary substantially across individuals just as the association of obesity measures with insulin resistance varies across individuals. Subsequently, the NCEP and the scientific statement from the American Heart Association and the National Heart, Lung, and Blood Institute [9] eliminated insulin resistance or obesity as a required trait (Table 39.1). Instead, at least three of five potential criteria need to be present to

TABLE 39.1 Metabolic syndrome definitions.

	Insulin resistance	Elevated glucose	Low HDL	Elevated triglycerides	Overweight	Elevated blood pressure	Urine albumin excretion
[12]NCEP-3 + traits	Not required, not a trait	≥ 100 mg/dL	<40 mg/dL (men), <50 mg/dL (women) or medication use	≥ 150 mg/dL or medication use	WC >102 cm (men), >88 cm (women)	≥ 130/85 mmHg or medication use	Not a trait
[122]WHO-2 + traits	Required: top 25th percentile in insulin levels or fasting glucose ≥ 110 mg/dL or 2 h glucose ≥ 140 mg/dL	See insulin resistance	<35 mg/dL (men); <40 mg/dL (women)	≥ 150 mg/dL	WHR >0.9 (men), >0.85 (women), or BMI ≥ 30 kg/m^2	≥ 140/90 mmHg	> 20 μg/min
[123]EGIR-2 + traits	Required: op 25th percentile in insulin levels	≥ 110 mg/dL	<40 mg/dL	≥ 180 mg/dL	WC ≥ 94 cm (men), ≥ 80 cm (women)	≥ 140/90 mmHg	Not a trait
[124]IDF-2 or more traits	Not required	≥ 100 mg/dL	<40 mg/dL (men); <50 mg/dL	≥ 150 mg/dL or on medications	Required: + WC ≥ 94 cm (men), ≥ 80 cm (women)	≥ 135/85 mmHg or medication use	Not a trait
[125]AACE	Not required	≥ 110 mg/dL; 2 h glucose ≥ 140 mg/dL	<40 mg/dL (men), <50 mg/dL (women) or medication use	≥ 150 mg/dL	Required: BMI >25 kg/m^2 or WC ≥ 102 cm (men), ≥ 88 cm (women)	≥ 130/85 mmHg or medication use	Not a trait

ACCE, American Association of Clinical Endocrinologists; *ATP-NCEP*, Adult Treatment Panel III from the National Cholesterol Education Program; *BMI*, body mass index; *EGIR*, European group for the Study of Insulin Resistance; *HD + If Asian*, different waist circumference thresholds should be utilized: ≥ 90 cm (men) or ≥ 80 cm (women); *IDF*, International Diabetes Federation; *WC*, waist circumference; *WHO*, World Health Organization; *WHR*, waist-to-hip ratio.

diagnose presence of metabolic syndrome. In contrast, the International Diabetes Foundation required the presence of obesity but not insulin resistance. The main problem with this strategy is that many adults with obesity do not have metabolic syndrome, especially those who are physically active [14]. Currently applied definitions do not account for family history of diabetes or CVD and do not address the organ manifestations of metabolic syndrome such as fatty liver disease and CKD factors associated with obesity and heightened mortality. It should be noted that the constellation of cardiovascular risk factors in adults with obesity was first recorded by a Swedish physician Eskil Kylin in 1923 and was conceptualized to describe [15] the end-organ damage from insulin resistance [15]. This early definition of metabolic syndrome included hyperuricemia, a trait that often predates the development of type 2 diabetes [16] and frequently accompanies CKD.

In 2009 a joint statement from the International Diabetes Federation Task Force on Epidemiology and Prevention and the National Heart, Lung, and Blood Institute along with several other organizations convened a conference to discuss the controversies regarding the terminology and criteria for metabolic syndrome diagnosis [17]. The members of all organizations agreed that metabolic syndrome represents the presence of multiple metabolic risk factors for both CVD and diabetes. However, the impact of obesity on overall health is not limited to the five metabolic syndrome traits defined by the NCEP [12]. Low HDL, glucose intolerance, increased triglycerides, abdominal adiposity, and elevated BP are traits that heighten CVD risk [9]. Metabolic syndrome also portends heightened risk for diabetes and in most individuals reflects insulin resistance. However, the constellation of metabolic syndrome traits is not always a reflection of insulin resistance and could instead reflect dietary patterns, sedentary lifestyle, aging, imbalance in estrogen and testosterone levels and genetic factors [9]. The ATP III metabolic syndrome definition is highly specific for insulin resistance but its sensitivity for hyperinsulinemia is overall low [18–20] because criteria do not address racial, sex, or age differences in the effects of adiposity on health and the strong genetic determinants of adiposity distribution and susceptibility to metabolic syndrome [21]. In addition, metabolic syndrome itself does not impart a higher predictive value for CVD risk compared to the sum of its individual components and thus the overall value of the metabolic syndrome definition remains questionable [22–24]. Regardless of the controversy, the metabolic syndrome may be viewed as a signal of high risk for diabetes, CVD and CKD, and signals a need for implementing nutritional and exercise strategies to reduce risk.

Metabolic syndrome and comorbidities

Based on the ATP III criteria, the overall prevalence of metabolic syndrome is now approximately 34% for both men and women [25]. The burden of metabolic syndrome is particularly high among Hispanic/Latino adults. In the Hispanic Community Health Study/Study of Latinos, a cohort study of 16,415 Hispanics from 6 Hispanic/Latino backgrounds, metabolic syndrome was present in over one-third of men and women and increased with age. The highest prevalence of metabolic syndrome was noted among the participants with a Puerto Rican Hispanic/Latino background at 41% [26].

Lifestyle modifications affect all metabolic syndrome risk factors; this supports the hypothesis that the risk factors are not independent of each other and are all mediated by one shared factor likely insulin resistance [9,27]. Insulin resistance combined with adiposity leads to abnormal lipid accumulation in skeletal muscle and the liver. In persons without enough adipose cells, excess calories must be stored elsewhere and this may include the liver. Despite the growth of fatty liver disease termed nonalcoholic fatty liver disease (NAFLD), metabolic syndrome criteria do not include fatty liver infiltration in the absence of heavy alcohol ingestion or NAFLD [12]. NAFLD describes a wide spectrum of disease ranging from fatty infiltration (nonalcoholic steatosis) to nonalcoholic steatohepatitis to cirrhosis and liver failure. While the amount of visceral adipose tissue correlates with the amount of hepatic adiposity, abdominal adiposity itself does not itself predict risk of NAFLD [28]. It appears that both adiposity and insulin resistance are necessary for the development of NAFLD because genetic mutations of insulin receptors that alter insulin resistance can prevent hepatic adiposity [29,30]. While adiposity is not necessary for NAFLD, 90% of NAFLD is associated with insulin resistance [28]. In healthy states the liver contains only 5% lipids in total weight but as the deposition of fat increases, the fatty hepatocyte starts to resemble brown adipose tissue [28]. Thus if excess caloric storage exceeds the capacity of the set number of adipocytes available, the liver acts as an additional storage depot for lipids similar to adipose tissue. In its early stages, NAFLD may be treated thru weight loss [31–33]. However, weight loss must be at least 5% of baseline weight to achieve improvements in liver histology. In one study, participants who lost at least 7% of baseline weight showed improved liver histology and significant improvements in steatosis despite the advanced state of liver disease [32].

Another storage depot for excess calorie storage is muscle. Intramyocellular lipid content is high among highly trained athletes because these fatty acids provide a quick energy source for physical activity [30]. High muscle lipid content in highly active individuals does not reflect insulin resistance. Among sedentary individuals, however, the intramyocellular lipid content correlates strongly with insulin resistance and exceeds the correlation of visceral fat content with insulin resistance [30,34]. Due to the confounding effects of exercise and the difficulties in accurate measurements, intramyocellular lipid content has not been utilized to quantify disease risk outside of research settings [30].

Chronic kidney disease

Metabolic syndrome is associated with increased risk of CKD defined by increased urine albumin excretion [35,36]. In healthy states, albumin normally accounts for less than 10% of the total urinary protein excretion and usually ranges from 2 to 10 mg/g of creatinine (10 mg/g) excreted [37]. Levels of urine albumin excretion exceeding this threshold of 10 mg/g are associated with increased risk of CVD, end-stage kidney disease, and mortality [38]. Increased urine albumin excretion is also hypothesized to reflect endothelial dysfunction, a central feature in metabolic syndrome. To understand the ties between insulin resistance, endothelial dysfunction, and increased urine albumin excretion, it is important to remember the key roles of insulin at the cellular level as shown in Fig. 39.1.

Fig. 39.1 demonstrates the normal function of insulin, the insulin receptor, and its effects on an endothelial cell. As shown in Fig. 39.1, insulin binds to an insulin receptor on the cell membrane. The inulin receptor is a transmembrane receptor that includes two extracellular alpha subunits and two transmembrane beta subunits linked by sulfide bonds [39]. Binding of insulin to the alpha subunits of the insulin receptor induces a conformational change that turns on kinase activity in beta subunits. This then leads to phosphorylation of the beta subunits on tyrosine residues and further activation of the intracellular tyrosine kinase domain. This phosphorylation is critically important for initiating the actions of the insulin itself [40]. Tyrosine phosphorylation of an insulin receptor via binding with insulin activates phosphoinositide 3-kinase (P13 kinase) that leads to phosphorylation of phosphatidylinositol 4,5 bisphosphate (PIP2) to yield phosphatidylinositol 3,4,5-triphosphate or PIP3. PIP3 is important for recruitment and activation of protein kinase B known as Akt, a serine, threonine kinase that regulates multiple cellular functions. Once Akt is activated via phosphorylation via the mammalian target of rapamycin complex 2, it recruits and stimulates several messengers to yield the main actions of insulin within the cell. For example, Akt leads to insertion of Glut4 transporters into the cell membrane wall—allowing glucose to enter the muscle cell [41]. Akt also phosphorylates and inactivates glycogen synthase kinase 3 that stimulates synthesis of glycogen from glucose and inhibits glycogeneolysis [42]. Activation of the mammalian target of rapamycin complex 1 by Akt leads to phosphorylation and inhibition of proteins kinases that

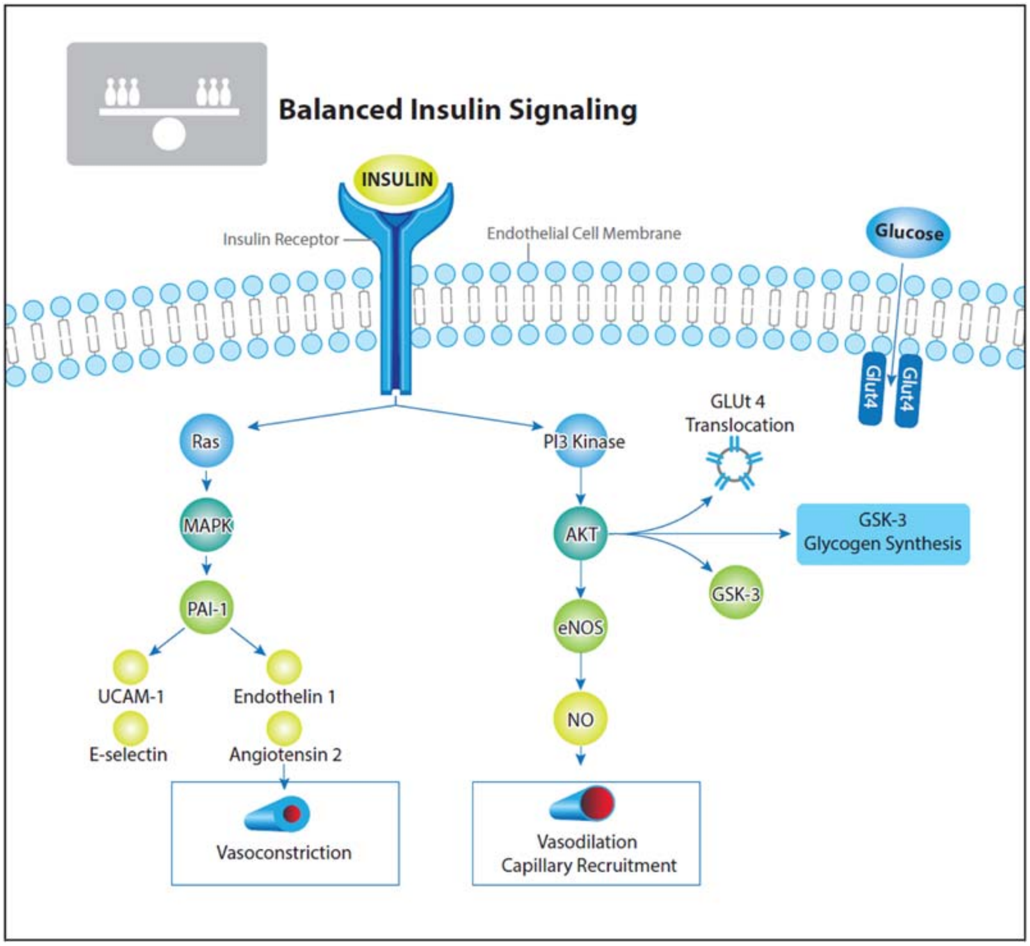

FIGURE 39.1 Figure depicts balanced insulin signaling in a healthy state. Insulin binds to insulin receptor and leads to activation of several G protein kinases and activation of both MAPK and AKT. MAPK activation leads to upregulation of vasoconstrictor production, for example, UCAM-1, endothelin-1, and angiotensin-2. Simultaneously, AKT activation leads to upregulation of endothelial nitric oxide synthase activity, increasing NO production. *AKT*, Protein kinase B; *eNOS*, endothelial nitric oxide synthase; *GSK-3*, glycogen synthase 3 kinase; *GLUT4*, glucose transporter type 4; *MAPK*, mitogen-activated protein kinase; *NO*, nitric oxide; *PAI-1*, plasminogen activator inhibitor-1; *PI3 kinase*, phosphoinositide 3-kinase; *UCAM-1*, intracellular adhesion molecule-1.

regulate expression of genes controlling protein synthesis and cell growth [39]. The phosphorylation and translocation from nucleus to cytoplasm of the transcription factors of the Forkhead Box O1 (FOXO1) by Akt blocks FOXO1 transcriptional activity. FOXO1 accelerates autophagy in response to cellular stress.

Thus the actions of insulin are not singularly focused on glucose transport but rather multiplex. Insulin is important for capillary recruitment and vasodilation to enhance cellular uptake of glucose and this occurs via the actions of endothelial nitric oxide synthase (eNOS). Activated Akt phosphorylates and activates eNOS. This is balanced by the actions of insulin on mitogen-activated protein (MAP) kinase. The activation of MAP kinase by tyrosine phosphorylation leads to upregulation of endothelin 1 production and expression of vascular cell adhesion molecule VCAM-1 and E-selectin-inducing more leukocyte endothelial interactions, endothelial cell growth, and vasoconstriction. In healthy states, mediators of vasoconstriction and cellular proliferation are balanced with mediators of vasodilation and inhibitors of cellular proliferation (Fig. 39.1). In the setting of insulin resistance, the MAP kinase arm is not affected and can even be upregulated. In contrast, the P13-Akt pathway is downregulated that leads to lower eNOS activation and less production of NO, a vasodilator (Fig. 39.2). In addition, the lack of cellular glucose uptake via Glut4 means that more glucose can enter the hexosamine biosynthetic pathway that normally metabolizes less than 3% of all glucose. The major end product of this pathway is uridine diphosphate N-acetylglucosamine (UDP-GlcNAc) and elevated levels of this can lead to modification of eNOS with *O*-GlcNAc known as O-GlcNAcylation [43] that inactivates eNOS leading to reduced levels of NO. Elevated levels of UDP-GlcNAc have been implicated in initiating and sustaining insulin resistance but this remains controversial.

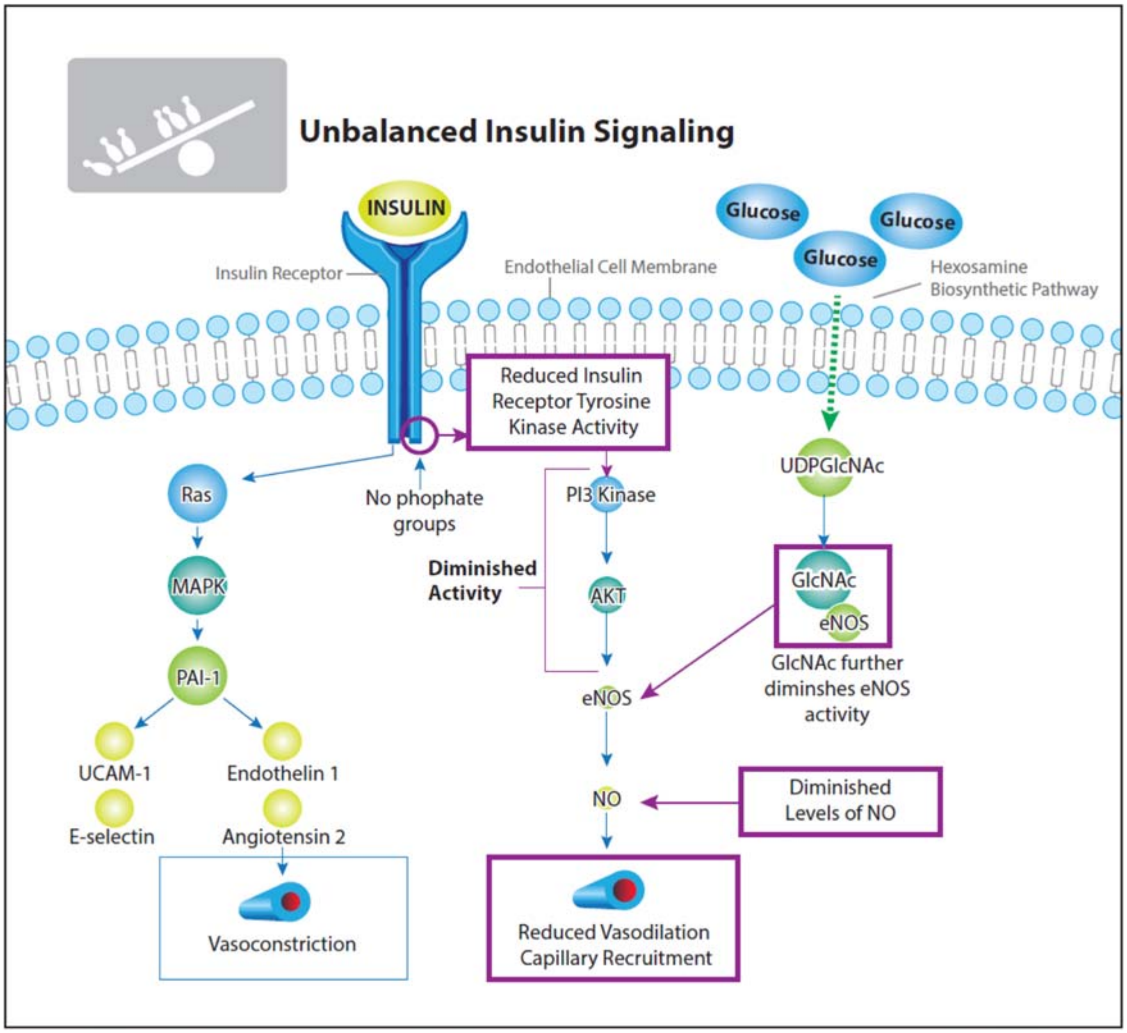
Unbalanced Insulin Signaling
INSULIN
Insulin Receptor
Endothelial Cell Membrane
Glucose
Glucose
Glucose
Hexosamine Biosynthetic Pathway
Reduced Insulin Receptor Tyrosine Kinase Activity
UDPGlcNAc
Ras
No phophate groups
PI3 Kinase
Diminished Activity
MAPK
AKT
GlcNAc
eNOS
GlcNAc further diminshes eNOS activity
PAI-1
eNOS
UCAM-1
Endothelin 1
NO
Diminished Levels of NO
E-selectin
Angiotensin 2
Vasoconstriction
Reduced Vasodilation Capillary Recruitment

FIGURE 39.2 Unbalanced insulin signaling in an insulin-resistant state. Insulin binds to insulin receptor but due to resistance, G protein kinases are less active. MAPK is not affected but AKT is not less phosphorylated and less active leading to lower GLUT4 translocation to cell membrane and less glucose entering the cell. This leads to more glucose entering the hexosamine biosynethetic pathway. The major endproduct of hexosamine biosynethic pathway is UDP-GlcNAc that modifies eNOS making it less active. Activation of AKT is also important for activating eNOS. The end result is less NO while vasoconstrictor production is not affected. *AKT*, Protein kinase B; *eNOS*, endothelial nitric oxide synthase; *GlcNAc*, N-acetyalglucosamine; *GLUT4*, glucose transporter type 4; *GSK-3*, glycogen synthase 3 kinase; *MAPK*, mitogen-activated protein kinase; *NO*, nitric oxide; *PAI-1*, plasminogen activator inhibitor-1; *PI3 kinase*, phosphoinositide 3-kinase; *UCAM-1*, intracellular adhesion molecule-1; *UDP-GlcNAc*, uridine diphosphate N-acetylglucosamine.

The imbalance between vasoconstrictors (endothelin) versus vasodilators (NO) creates a vicious cycle because the vasoconstriction inhibits glucose uptake due to lower capillary recruitment and decreased local blood flow that is normally mediated via the actions of insulin [44,45]. To interrupt this cycle, eNOS activity needs to be upregulated; eNOS phosphorylation by Akt kinase can be heightened with statin medications and by adiponectin and via interruption of insulin resistance via reduction in caloric intake and weight loss (Table 39.2). Thus insulin resistance is marked by an imbalance of vasoconstrictors, vascular cell adhesion, and proliferation versus vasodilators. This leads to endothelial dysfunction in endothelial cells.

The actions of insulin resistance can also be seen within podocytes that also have insulin receptors. High extracellular glucose can induce podocyte apoptosis and both insulin resistance and glucose toxicity on podocyte function and autophagy have been implicated in the etiology of diabetic nephropathy [46,47]. Cross-sectional studies have demonstrated an association between increased urine albumin excretion and visceral adiposity, especially in adults with type 2 diabetes [48–50]. However, this association between visceral adiposity and increased urine albumin excretion may be due to the effects of elevated BP alone, and not a result of metabolic syndrome per se [51,52].

TABLE 39.2 Factors that influence endothelial nitric oxide synthase (eNOS) phosphorylation by Akt activity.

Factor	Mechanism
Weight loss/Caloric restriction	Interrupts insulin resistance via reducing glucose entering hexosamine biosynthetic pathway and reducing production of uridine diphosphate N-acetylglucosamine, an inhibitor of eNOS and via upregulation of adiponectin production
Adiponectin	Adiponectin phosphorylates eNOS at Ser^{1177} and activates AMP-activated protein kinase
Statin medications	Blocks formation of many compounds, such as farnesylpyrophosphate and geranylgeranyl pyrophosphate, nonsteroidal isoprenoid compounds, that inactivate G-proteins important for upregulating eNOS activity

The link between obesity and kidney disease is not limited to increased urine albumin excretion. Obesity, especially morbid obesity, strongly impacts risk of all stages of CKD. Obesity, especially morbid obesity, appears to be a very strong risk factor for future risk of end-stage renal disease but this association appears strongest if obesity occurs during the early years of adulthood. One of the largest cohort studies in the United States examined 320, 252 adults who were age 18–34 years when they participated in a health screening exam during years 1964 and 1985. After 15–34 years of follow-up, morbid obesity (BMI ≥ 40 kg/m^2) was associated with a sixfold higher risk of kidney failure compared to an ideal BMI (18.5–24.9 kg/m^2) [53]. A cohort that followed adolescents thru adulthood also found similar associations of morbid obesity with kidney failure [54]. In contrast, obesity occurring later in life has not demonstrated strong associations between obesity and kidney failure risk [55–57]. The age modification of kidney disease risk associated with obesity may be due to cumulative exposure to high insulin and glucose levels if obesity begins at an early age. This hypothesis is supported by studies showing that associations of obesity with kidney failure risk is limited to individuals with metabolic syndrome and/or elevated BP [55,58]. In the REasons for Geographic and Racial Differences in Stroke (REGARDS) study, metabolic syndrome was a strong modifier of the association of obesity with kidney disease. Among 21,840 REGARDS participants with a mean baseline age of 65 years and followed for 6.3 ± 1.3 years, 247 developed kidney failure. Obesity defined by a BMI ≥ 30 kg/m^2 was associated with a twofold higher risk for kidney failure compared to an ideal BMI of 18.5–24.9 kg/m^2 after adjustment for covariates. However, this association of higher kidney failure risk with obesity status was only noted in the REGARDS participants with metabolic syndrome [55]. Similar findings were also noted in a large cohort of adults followed for risk of incident CKD [59]. Measures of obesity were not associated with incident CKD in the absence of metabolic syndrome traits.

Measures of abdominal obesity such as increased waist circumference or waist-to-hip ratio are more consistently associated with kidney disease risk compared to BMI [56,60,61]. In addition, multiple studies have consistently demonstrated an association of abdominal obesity and increased urine protein (mainly albumin) excretion in several types of populations [48,49,62]. Differences in kidney disease risk across obesity measures are likely due to the fact that waist circumference and waist-to-hip ratio reflect visceral fat, a strong risk factor for development of insulin resistance, while BMI includes visceral fat and lower body fat. Even with these visceral adiposity measures, obesity among older adults (e.g., 60 years and older) only modestly increases the risk of kidney failure and associations appear largely driven by hypertension and diabetes. In contrast, if obesity, especially morbid obesity, initiates during adolescence or young adulthood then the individual is exposed to metabolic syndrome traits for a prolonged period of time, heightening kidney disease risk.

Metabolic syndrome defined by the NCEP ATP III criteria is associated with moderately increased odds of both incident and prevalent CKD [63–65]. Odds of CKD defined as an estimated glomerular filtration rate (eGFR) <60 mL/min/m^2 or a spot urine albumin/creatinine ratio (30–300 mg/g) increased linearly with the number of metabolic syndrome traits from 2.21 [95% confidence interval (CI), 1.16–4.24] with 2 traits to 5.85 (95% CI, 3.11–11.0) with 5 traits compared to individuals with no traits. In a cross-sectional analysis of a population-based survey of the US population [64], similar findings were noted in the Jackson Heart Study, a cohort of Among African American adults. Among the Jackson Heart cohort, elevated BP, triglycerides, fasting blood glucose, and abdominal obesity were all significantly associated with increased odds of CKD [66]. However, the presence of metabolic syndrome was associated with a 2.2-fold increased odds of CKD (95% CI, 1.78–2.78). Among persons with established CKD such as the African-American Study of Hypertension and Kidney Disease, in which all trial participants had CKD at baseline, the presence of metabolic syndrome was associated with higher levels of urine protein excretion at baseline but not with CKD progression [67]. In the Strong Heart Study a cohort of American Indian adults demonstrated that the presence of metabolic syndrome was associated with heightened risk of incident CKD but this association was largely driven by development of diabetes and hypertension [68]. Most studies find moderate associations of metabolic syndrome with incident CKD. A metaanalysis published in 2011 found eleven studies with a total of 30,146 adults followed over time for CKD defined as an eGFR $< 60\ \mathrm{mL/min/1.73\ m^2}$. The presence of metabolic syndrome was associated with a 1.6-fold increased odds of CKD (95% CI, 1.3, 1.8) and the higher the number of metabolic syndrome traits present, the stronger the association (trend P value = .02). The strongest association with CKD for a given metabolic syndrome trait was noted for elevated BP with an odds ratio (OR) of 1.6 (95% CI 1.3, 2.0) and lowest for abdominal obesity (OR 1.2; 95% CI 1.1, 1.3), and impaired fasting glucose (OR 1.1; 95% CI 1.0, 1.3). The metaanalysis also reported that three studies showed that metabolic syndrome was associated with an increased risk for development of increased urine albumin excretion [69].

Information on the link between metabolic syndrome and CKD risk remains fairly limited because most cases of kidney disease evolve over decades and not within a few years so cohort studies need extended follow up to fully evaluate potential risk factors. The metabolic syndrome trait most consistently and strongly associated with loss of eGFR over time in cohort studies is elevated BP. The Atherosclerosis Risk in Communities Study with 30 years of follow-up has demonstrated that the presence of hypertension is associated with a faster rate of eGFR decline and higher risk of CKD even after adjustment for diabetes status [70]. We also know that higher BP among adults with diabetes is associated with a higher risk of decreased GFR, especially in the presence of increased urine albumin excretion [71,72]. Based on metaanalyses of well-designed clinical trials, a systolic BP (SBP) target <130 mmHg is now recommended for individuals with nondialysis dependent CKD [73,74]. The evidence supporting this BP target is strongest for persons without diabetes mellitus [75] or persons with moderate to severely increased urine albumin excretion [72,73]. Among individuals with diabetes, intensive glucose control lowers risk of developing increased urine albumin excretion, especially during the early stages of diabetes. The Action to Control Cardiovascular Risk [76] in Diabetes study showed small but significant reductions in the absolute risk of developing increased urine albumin excretion with intensive glucose lowering. A metaanalysis of intensive glucose control studies in type 2 diabetes mellitus (T2DM) 1 [77] with 28,065 adults with type 2 diabetes followed for 2–15 years showed significantly reduced risk of both moderately increased [relative risk (RR) = 0.86, 95% CI: 0.76–0.96] and severely increased urine albumin excretion (RR = 0.74, 95% CI: 0.65–0.85) with intensive glucose control [median hemoglobin A1c (HbA1c) 6.4%–7.4%]. To date, intensive glucose control has not been associated with reduced risk of kidney failure although data suggest trends toward benefits with intensive control [78]. Several studies have also shown that even among adults without established diabetes, higher HbA1c values are associated with faster rate of age-associated decline in the eGFR [79,80]. In a secondary analysis of the Outcome Reduction with Initial Glargine Intervention trial that included 12,537 people with T2DM or prediabetes followed for 6.2 years, RR of kidney failure was 54% higher (95% CI; 24%, 91%) for every 1% higher baseline HbA1c values among trial participants. In addition, long-term glucose control with pancreas transplant had demonstrated reversibility of diabetic nephropathy posttransplant [81], but this was only seen histologically after 10 years of normal glucose levels [82].

Higher urine albumin or protein excretion is associated with faster GFR decline in the setting of kidney disease [83–85]. While BP-lowering will lower urine protein excretion [71,86], caloric restriction and weight loss are also effective interventions regardless of BP because weight loss improves insulin resistance via downregulation of fatty acid mobilization [87] and reductions in inflammation and renin–angiotensin–aldosterone system activation [88]. High concentration of circulating free fatty acids (FFAs) promotes insulin resistance by competitively inhibiting glucose uptake by muscle. For example, urine protein excretion decreases rapidly after bariatric surgery among morbidly obese adults likely because caloric intake during the first 6 months is markedly reduced [89]. Declines in urine protein excretion occur as early as 1 month with caloric restriction. A metaanalysis of 13 studies of weight-loss interventions, including dietary restriction, exercise, antiobesity medications, and surgery with a total of 522 participants [90] showed that urine protein or albumin excretion decreased significantly with weight loss, regardless of the intervention. On average, urine protein excretion decreased by 110 mg (95% CI, 60–160 mg, $P < .001$) and urine albumin excretion decreased by 1.1 mg (95% CI, 0.5–2.4 mg, $P = .011$) per kilogram of weight loss, for both surgical and medical interventions.

One cellular metabolic pathway that elucidates mechanisms whereby caloric restriction reduces protein excretion is upregulation of adiponectin that improves insulin sensitivity at the cellular level. Adiponectin receptors reside on podocytes and may improve function and survival [91,92]. Adiponectin expression is upregulated via the Sirt1-Foxo1 pathway [93]. Sirt1, an NAD$^+$-dependent deacteylase, expressed in the renal inner medulla, activates the cell cycle protein Foxo1 [93,94], which then forms a transcriptional complex with C/EBPα at the adiponectin gene promoter site and turns on gene expression. Adiponectin can upregulate eNOS activity via phosphorylation of eNOS at Serine residue 1177 similar to actions of Akt previously described [95]. Increased activity of eNOS leads to higher NO levels and increased blood flow and vasodilation and can reduce BP.

Treatment of metabolic syndrome

Because metabolic syndrome confers such a strong risk for cardiovascular and kidney diseases and future development of type 2 diabetes, the syndrome should be addressed with a diet and lifestyle intervention. The best evidence we have for amelioration of metabolic syndrome with a lifestyle intervention is from the Diabetes Prevention Program (DPP). The DPP [96] randomized persons at high risk for type 2 diabetes to either an intensive lifestyle intervention, metformin, or a placebo. After 3 years, persons in the intensive lifestyle intervention had a 58% lower risk of developing type 2 diabetes compared to the placebo group. The annual risk of developing type 2 diabetes was 5% in the lifestyle intervention group and 11% in the placebo group. The benefits of lifestyle changes were most prominent among persons age 60 years and older in whom risk of developing type 2 diabetes was reduced by 71% compared to placebo. Metformin use was also associated with reduced risk of developing type 2 diabetes compared to placebo. Risk of developing type 2 diabetes was 31% lower compared to placebo and effects were strongest among women with a history of gestational diabetes and among those with a baseline BMI of 35 kg/m^2 and higher. After the trial ended, participants were then followed for the development of type 2 diabetes. After 15 years of follow-up, 55% and 56% of participants assigned to the lifestyle intervention and metformin, respectively, developed type 2 diabetes compared to 62% of participants assigned to placebo during the trial [97]. Similar findings have been shown in similar trials completed outside the United States in which diet and lifestyle changes led to approximately 30%−40% lower risk of type 2 diabetes over 10−20 years [98,99].

Lifestyle interventions for metabolic syndrome must include both weight loss and physical activity. In the DPP trial, weight loss goals were 7% or higher of baseline weight and physical activity goals were set at 150 minutes of vigorous activity such as brisk walking to expend approximately 700 kcal/week. Weight loss recommendations were 1−2 lbs/week with reducing between 500 and 1000 cal/day depending on the baseline body weight.

The type of diet may also help reduce risk of type 2 diabetes as implementation of a Mediterranean diet high in monosaturated fats such as olive oil and low in saturated fats has been shown to reduce risk of type 2 diabetes and kidney disease [100]. In addition, observational studies suggest that persons with high adherence to a Mediterranean diet have a lower risk of developing metabolic syndrome [101] The Western diet is high in processed foods, sugar, and fat and these factors all increase risk of developing metabolic syndrome and T2DM.

Metformin was approved for the prevention of type 2 diabetes by the FDA in 2017 and is recommended by the American Diabetes Association for diabetes prevention in high-risk individuals [102]. Metformin is a biguanide that inhibits hepatic glucose output. However, only 50% of the drug is absorbed and reaches the liver while the other 50% accumulates in the gut. Within the gut, metformin alters the microbiome by increasing longevity of gut bacteria that consume calories within the intestine [103].

Other medications that may be considered for addressing metabolic syndrome and insulin resistance are the thiazolidinediones (TZDs). The TZD class of glucose-lowering medications promotes insulin sensitivity by activating the peroxisome proliferator-activated receptor-gamma that leads to upregulation of genes involved with lipid metabolism and adipogenesis. The use of this class of drugs is associated with reduction in FFAs and urine albumin excretion in adults with type 2 diabetes via amelioration of insulin sensitivity in liver, muscle, and fat tissue [104]. Trials of TZDs have not shown that this class of medications slow kidney function decline or reduce risk of incident CKD or kidney failure. The use of this medication has been impeded by its risks of sodium retention and weight gain leading to heart failure.

Another class of drugs, the glucagon-like peptide-1 (GLP-1) receptor agonists, may become increasingly more relevant for management of metabolic syndrome [105]. GLP-1, a peptide hormone, is secreted in response to circulating glucose and increases pancreatic insulin secretion and decreases glucagon secretion. Normally, GLP-1 is rapidly degraded by the enzyme dipeptidyl peptidase IV but the GLP-1 receptor agonists are resistant to degradation by this enzyme. Receptors for GLP-1 reside in multiple tissues in the body, including the hypothalamus, pancreas, and kidney. Currently, drugs in this class are approved for use in persons with type 2 diabetes but one drug, liraglutide, is approved for management of obesity by the Federal Drug Administration. These drugs bind to receptors in the hypothalamus and increase satiety and decrease appetite. Liraglutide use is generally associated with weight loss (~6 kg) and other GLP-1 agonists can also lead to weight loss, albeit less. This drug class is also associated with an approximate 5 mmHg drop in SBP and diastolic BP and a reduction in serum triglycerides. Effects on metabolic syndrome traits are likely mediated mainly via weight loss.

While this drug class is not approved for treatment of metabolic syndrome, metabolic syndrome traits may be positively affected with GLP-1 agonists. Animal models that lack GLP-1 receptors show higher urinary albumin levels and mesangial expansion in the setting of diabetes and this is attributed to higher levels of oxidative stress due to increased glomerular superoxide. Liraglutide in animals lacking GLP-1 receptors ameliorates the effects of hyperglycemia in the kidney by suppressing superoxide production. In the Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results trial, the use of liraglutide was associated with a 22% lower risk of a primary kidney endpoint defined as the development of macroalbuminuria, doubling of serum creatinine and eGFR < 45 mL/min/1.73 m^2, the need for renal replacement therapy, and death from renal causes (95% CI: 8%, 33%; $P = .03$) compared to placebo. However, most of the renal endpoints in this trial were new-onset macroalbuminuria. The renal benefit of liraglutide was mainly derived from a 26% significant reduction in new-onset macroalbuminuria (95% CI 9%, 40%) without any significant changes in eGFR. The use of liraglutide in this trial was associated with a 2.3 kg weight loss and a drop of 1.2 mmHg in SBP. Similar findings were noted in the Trial to Evaluate Cardiovascular and other long-term outcomes with semaglutide (SUSTAIN-6) with 46% reduction (95% CI 23%, 63%; $P < .001$) in risk of developing macroalbuminuria relative to placebo among adults with type 2 diabetes [106].

Another drug class with demonstrated benefits on metabolic syndrome traits is the dipeptidyl peptidase-4 inhibitors. This class of drugs increases beta cell mass and function and improves liver, muscle, and adipose tissue insulin sensitivity [107]. While fatty acid oxidation is increased with DPP-4 inhibitors, hepatic triglyceride synthase is reduced leading to lower triglyceride levels and decreased lipogenesis. These drugs also delay gastric emptying potentiating satiety leading to decreased caloric intake. A pooled analysis of 13 clinical trials of the DPP-4 inhibitor linagliptin versus placebo [108] with follow-up ranging from 12 to 76 weeks showed linagliptin reduced risk of developing a kidney endpoint defined as new-onset micro or macroalbuminuria, loss of baseline eGFR >50%, acute renal failure, or death from any cause. The absolute risk difference in kidney endpoints was 2.8% with lower risk in the linagliptin group (HR = 0.84; 95% CI: 0.72−0.97, $P = .02$). Currently, the DPP-4 inhibitors are only approved for treatment of type 2 diabetes.

Another class of drugs to consider for management of metabolic syndrome in certain patients is the sodium−glucose cotransporter type 2 (SGLT2) receptor inhibitors, especially for patients with a high risk of kidney failure. One of these drugs, canagliflozin, was the first diabetes drug approved by the Federal Drug Administration for the prevention of cardiovascular events. The SGLT2 receptor is found in the early proximal tubule and is responsible for mediating sodium and glucose reabsorption. When SGLT2 is inhibited, glucose and sodium are excreted in the urine. Due to the loss of sodium, which is sensed by the macula densa in the juxtaglomerular apparatus, intraglomerular pressure is reduced due to afferent arteriolar vasoconstriction. The loss of glucose leads to lower insulin levels and these effects along with sodium loss explain the diuretic effects of this drug class. The diuresis leads to weight loss and lowered BP. In the CVD safety trial of empagliflozin (EMPA-REG), use of empagliflozin in 7020 adults with type 2 diabetes and high CVD risk showed significantly lower risk of kidney outcomes defined as progression to macroalbuminuria, doubling of serum creatinine level associated with an eGFR < 45 mL/min/1.73 m^2, initiation of renal replacement therapy and death from renal disease. Absolute risk reduction of renal endpoints with empagliflozin was 6.1%—with events occurring in 12.7% of those treated with empagliflozin and 18.8% in the placebo group ($P < .001$). Similar to other trials of glucose-lowering medications, most renal endpoints were increased urine albumin excretion, and in the EMPA-REG trial, reduction in new-onset macroalbuminuria was responsible for most of the renal benefits with empagliflozin. In animal models, this drug class shows reduction in oxidative stress, inflammation, fibrosis, and tubular senescence that would provide direct kidney benefits [109]. A metaanalysis of four trials of SGLT2 inhibitors in 38,723 adults with type 2 diabetes [110], SGLT2 inhibitors reduced the risk of dialysis, transplantation, or death due to kidney disease by 33% (95% CI 14%, 48%, $P = .0019$) relative to placebo. Risks of both kidney failure (RR = 0.65, 0.53−0.81, $P < .0001$) and acute kidney injury (RR = 0.75, 0.66−0.85, $P < .0001$) were significantly reduced with SGLT2 inhibitor use. Benefits were consistent across baseline urine albumin excretion levels and use of renin−angiotensin system inhibitors. Because these drugs do not increase insulin secretion, they may have benefits in adults without established diabetes and could reduce kidney disease risk in the setting of metabolic syndrome.

The CREDENCE Trial [111] examined canagliflozin in adults with type 2 diabetes and kidney disease, defined as an eGFR 30−90 mL/min/1.73 m^2 and albumin-to-creatinine ratio 300–5000 mg/g and receiving treatment with a renin–angiotensin system blocker. The trial was stopped early after an interim analysis showed the risk of kidney failure and cardiovascular events was 30% (95% CI, 18%, 41%; $P = .00001$) lower in the canagliflozin group than in the placebo group at a median follow-up of 2.62 years. Kidney endpoints were defined as development of kidney failure, doubling of baseline serum creatinine level, or death from renal causes. Risk of the composite renal outcome was 34% (95% CI, 18%, 47%; $P < .001$) relative to placebo while risk of kidney failure was 32% lower (95% CI, 14%, 46%; $P = .002$) relative to placebo. Risk of cardiovascular events defined as cardiovascular death, myocardial infarction, or stroke was reduced by 20% (95% CI, 5%, 33%; $P = .01$) while hospitalization for heart failure was reduced by 39% (95% CI, 20%, 53%; $P < .001$) relative to placebo. In contrast to the CREDENCE Trial, the study to evaluate the effects of dapagliflozin on renal outcomes and cardiovascular mortality in patients with CKD NCT03036150 is enrolling patients with both diabetic and nondiabetic CKD and will help determine whether this drug class shows similar benefits to adults with type 2 diabetes and may provide evidence for its use in metabolic syndrome.

Finally, the importance of lifestyle modifications, including dietary changes, cannot be overstated for those with metabolic syndrome and obesity. Diets that emphasize the consumption of whole, plant-based foods have been repeatedly linked with weight loss, likely due to the presence of fiber in plant-based foods and other differences [112]. Several observational studies have shown that increasing fiber consumption is directly associated with weight loss [113]. For example, in one study, every 1-g increase in dietary fiber intake was associated with a 0.25-kg reduction in body weight [114]. A systematic review and metaanalysis of clinical trials found that vegetarian diets were associated with a 3.4-kg weight loss in an intention-to-treat analysis, with larger weight losses being achieved in those who completed the trials [115]. Fiber's ability to facilitate weight loss is likely related to the lower caloric density of those foods and increases in satiety hormones like GLP-1 and peptide YY (both of which are increased by soluble fiber) [116].

In addition to weight loss, the consumption of plant-based foods may also have benefits for kidney-related outcomes. In the Adventist Health Study-2, researchers found that among nearly 73,000 participants followed over an average of 5.8 years, those consuming a vegetarian diet had a 52% reduced risk (95% CI, 8%, 82%) of kidney disease associated mortality [117]. Consumptions of diets emphasizing plant-based foods have also been associated with less proteinuria and a lower risk of CKD [118,119]. Benefits of plant-based foods may also occur with only partial inclusion of these foods into a diet. In a randomized, controlled trial of the use of fruits and vegetables for metabolic acidosis secondary to CKD, Goraya et al. found reductions in BP, weight, and albuminuria along with improvements in metabolic acidosis comparable to oral bicarbonate with as little as two to four servings of fruits and vegetables per day [120]. Other benefits of a plant-based diet in kidney disease may include reductions in serum phosphate levels and uremic toxins [121].

In summary, metabolic syndrome is defined by the presence of multiple traits that occur due to caloric consumption exceeding energy expenditure. Persons with a genetic predisposition to store these excess calories in the abdomen and those with reduced fat storage capacity have increased susceptibility to develop metabolic syndrome. Metabolic syndrome is associated with increased risk of CKD. Weight loss, dietary changes, and exercise remain the cornerstone treatment for metabolic syndrome. Medications that improve insulin sensitivity or impair kidney glucose reabsorption may also help ameliorate the impact of metabolic syndrome on kidney disease risk.

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CHAPTER

40

Nutritional and metabolic management of obesity and the metabolic syndrome in patients with chronic kidney disease

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Introduction

Obesity has in recent decades emerged as a premier global health problem. In 2016 more than 1.9 billion adults worldwide were overweight, with 650 million of these being obese [1]. Individuals with or at risk for chronic kidney disease (CKD) are also adversely affected by this trend. In fact, obesity is arguably replacing uremia-related undernutrition as the main nutritional problem facing patients with CKD, at least in the United States [2]. Obesity is a wellspring not only a wellspring for many of the most common and important risk factors for CKD but is also independently associated with the development and progression of CKD. It is not an exaggeration to state that CKD in modern times is to a large degree a complication of obesity. Consequently, strategies to mitigate obesity may help in managing and treating CKD. This chapter will review the epidemiology, trends, pathophysiology, and management strategies for obesity-related kidney disease and the metabolic syndrome, focusing primarily on individuals with CKD who have not yet reached end-stage kidney disease (ESKD).

Magnitude of the obesity crisis

Obesity is undoubtedly a scourge of modernity [1]. Though traditionally a problem limited to affluent Western societies, obesity has also become increasingly common in developing nations [3]. It is evident that obesity has greatly affected the CKD population as well. Between 2011 and 2014 the prevalence of obesity in US adults with CKD was 44.1% [2]. This represents a 5% absolute increase in obesity compared to the preceding 12 years (and a higher prevalence than the 37.9% seen in the general populace during that period [4]). Worse, over 25% of CKD patients manifested more severe degrees of obesity.

A plausible explanation for such findings is that the growing abundance of inexpensive, calorie-dense foodstuffs combined with an increasingly sedentary lifestyle affect individuals with CKD at least as much as the general populace. The fact that CKD patients are limited in their physical activity due to physical impairements may further compound the problem. However, the precise cause of the obesity crisis is still open for debate [5].

Defining obesity in persons with chronic kidney disease

The definition of "excess" body fat is somewhat arbitrary and lacks a validated threshold. Though a number of techniques are available to accurately measure body fat content and/or patterns of unhealthy fat deposition, such as neutron activation analysis, dual-energy X-ray absorptiometry, bioelectrical impedance, air-displacement plethysmography, and computed tomography, they are used primarily for research purposes.

In clinical practice, obesity is determined by simple measurements that "define" excess body fat in a manner that is partly derived from their association with clinical risk [6]. The most commonly used marker of obesity in patients with CKD is the body mass index (BMI), which is a ratio of weight to height [i.e., weight (kg) divided by height squared (m^2)].

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TABLE 40.1 Classifying overweight and obesity according to body mass index (BMI), waist circumference, and associated disease risk.

			Disease risk[a] relative to normal weight and waist circumference	
Classification	**BMI (kg/m^2)**	**Obesity class**	**Men ≤102 cm/Women ≤88 cm**	**Men >102 cm/Women >88 cm**
Underweight	<18.5		–	–
Normal weight[b]	18.5–24.9		–	–
Overweight	25.0–29.9		Increased	High
Obesity	30.0–34.9	I	High	Very high
	35.0–39.9	II	Very High	Very High
Extreme obesity	≥40	III	Extremely high	Extremely high

[a] *Disease risk for type 2 diabetes, hypertension, and cardiovascular disease.*

[b] *Increased waist circumference can increase risk even in persons of normal weight.*

Adapted from National Institutes of Health: National Heart, Lung, and Blood Institute. Clinical guidelines on the identification, evaluation, and treatment of overweight and obesity in adults. Bethesda, MD: National Institutes of Health: National Heart, Lung, and Blood Institute; 1998.

Simple to calculate and easy to employ, the BMI is a reasonably good indicator of total body fat content in the general population as well as in patients with CKD [6–8]. One study of 77 patients with an estimated mean glomerular filtration rate (eGFR) of 40 mL/min/1.73 m^2 found that a BMI greater than 30 kg/m^2 had a 100% positive predictive value for detecting obesity compared with a reference body composition method, while its negative predictive value was only 30% [7]. That is, a high BMI confirmed obesity while a lower BMI did not exclude obesity. This study highlights some of the limitations of BMI, including that it cannot distinguish lean from fat mass, peripheral from central/visceral fat, or volume excess from fat excess. These limitations have spurred interest in alternative anthropometric measurements such as waist circumference and waist-to-hip ratio that can detect excess visceral fat in a manner that the BMI cannot. Visceral fat is currently considered an important causal risk factor for insulin resistance, the metabolic syndrome, and cardiovascular disease [9]. Studies suggest that these alternative metrics add additional prognostic information in the CKD population [10–12]. Table 40.1 shows the classification of overweight and obesity and associated disease risk by BMI and waist circumference.

Clinical indicators of kidney disease in obese individuals

The two most important clinical markers of kidney function and disease are the GFR and proteinuria (or albuminuria) [13]. The GFR is most accurately measured by plasma or urinary clearance of inulin or other exogenous markers [14]. However, because direct measurement is cumbersome, time-consuming, and too costly for routine use, most clinicians and many researchers rely on creatinine-based formulas such as the Cockcroft–Gault [15], Modification of Diet in Renal Disease [16], and CKD Epidemiology Collaboration [17,18] equations to estimate GFR. Such equations should be used with caution in individuals who are obese or whose weights are fluctuating for the following reasons: first, estimating equations work reasonably well in the populations they were derived in, but none of the equations were derived in primarily obese populations, which explains why their accuracy is reduced in that population [19–22] and in patients with fluctuating weight. Second, estimating equations rely heavily on serum creatinine as an endogenous filtration marker. Serum creatinine is generated primarily from muscle so all other things being equal the greater the muscle mass, the higher the serum creatinine. Therefore any change in muscle mass as a result of weight gain or loss will influence serum creatinine generation and make it difficult to differentiate true effects on glomerular filtration from spurious changes in serum creatinine. An alternative endogenous filtration marker in obese patients is serum cystatin C. Cystatin C is more closely associated with measured GFR than creatinine in very obese individuals [23]. However, even cystatin C may be influenced by body mass [24,25].

Third, GFR-estimating equations usually include an adjustment for body surface area to equalize differences in body size between individuals. This indexing strategy is based upon the observed relationship in mammals that GFR is proportional to body size [26] that is presumably related to the fact that the kidney modifies its excretory (e.g., filtration) capabilities based upon the amount of metabolic by-products generated by the body [27,28]. The use of body surface adjustments in obese individuals presents challenges because it is lean and not fat mass that generates most metabolic waste so adjusting for lean *and* fat mass introduces systemic bias and error [29]. Because of these pitfalls, clinical trials should ideally directly measure rather than estimate and/or index GFR for body size in individuals who are gaining or losing weight [23,30].

Proteinuria or albuminuria can be measured from a 24-hour urine collection or estimated from a spot urine protein (or albuminuria)-to-creatinine ratio. While either method is acceptable in obese individuals, the latter is susceptible to bias when used for serial measurements during weight change because urine creatinine is dependent upon muscle mass and will change with weight gain or loss. It will therefore be difficult to distinguish if a rise in the urine protein-to-creatinine ratio after weight loss represents a true increase in proteinuria or alternatively reflects a reduction in urinary creatinine. In the setting of weight change, a 24-hour urine collection is, therefore, the preferred method of measurement.

The metabolic syndrome

The risk that obesity confers is heightened by the presence of additional risk factors like elevated blood pressure, dyslipidemia, and insulin resistance ± glucose intolerance that are together known as "the metabolic syndrome" [31]. Originally designed to identify a set of risk factors for cardiovascular disease that cluster together, the metabolic syndrome is associated with increased risk for development of proteinuria/albuminuria [32], development and progression of CKD [33–35], and ESKD [36]. There is some disagreement as to whether obesity remains a risk factor for CKD in obese patients who do not manifest the "metabolic syndrome" phenotype and who are "metabolically healthy" [37–39]. In addition, there is an ongoing debate over the best definition and usefulness of the metabolic syndrome classification system. There are at least two definitions of the metabolic syndrome, each of which differs slightly from the other [31,40] (Table 40.2).

Moreover, the definition of metabolic syndrome has been criticized for, among other things, its ambiguous criteria and ill-defined thresholds, the uncertainty of using insulin resistance as a unifying etiology, and its questionable value in defining cardiovascular risk and in diagnosing and treating patients [41].

Obesity and risk for chronic kidney disease

A consensus has emerged from the medical literature indicating that obesity accounts for a large proportion of CKD. Population attributable risk analyses estimate that approximately one-fifth to one-fourth of kidney disease cases could be prevented by eliminating overweight and obesity, a proportion that would invariably be much higher if the intermediate CKD risk factors diabetes and hypertension were included [42]. Another population-based study reports that the lifetime risk of CKD is 32.5%, 37.6%, and 41% in persons who are normal weight, overweight, or obese, respectively [43].

Weight gain or obesity are independent predictors for the development of proteinuria, kidney stones, acute kidney injury, and CKD in the general population [44–50] and in higher risk groups like individuals with prehypertension [51]. These observations include

TABLE 40.2 Definitions of the metabolic syndrome.

ATP III definition
Any three or more of the following criteria:
1. Waist circumference >102 cm in men and >88 cm in women
2. Serum triglycerides ≥ 1.7 mmol/L
3. Blood pressure ≥ 130/85 mmHg
4. HDL cholesterol <1.0 mmol/L in men and <1.3 mmol/L in women
5. Serum glucose ≥ 6.1 mmol/L (≥5.6 mmol/L may be applicable)
WHO definition
Diabetes, IFG, IGT, or insulin resistance (assessed by clamp studies) and at least two of the following criteria:
1. Waist-to-hip ratio >0.90 in men or >0.85 in women
2. Serum triglycerides ≥ 1.7 mmol/L or HDL cholesterol <0.9 mmol/L in men and <1.0 mmol/L in women
3. Blood pressure ≥ 140/90 mmHg
4. Urinary albumin excretion rate >20 μg/min or albumin-to-creatinine ratio ≥ 30 mg/g

ATP, Third Report of the National Cholesterol Education Program's Adult Treatment Panel; *HDL*, high-density lipoprotein; *IFG*, impaired fasting glucose; *IGT*, impaired glucose tolerance; *WHO*, World Health Organization.

With permission from Grundy SM, et al., Definition of metabolic syndrome: report of the National Heart, Lung, and Blood Institute/American Heart Association conference on scientific issues related to definition. Circulation 2004;109(3):433–8.

a wide range of ethnic groups and ages. One such study of a global database that included over 5.4 million healthy individuals found the risk of a decline in the GFR progressively and independently increased as the BMI rose above 25 kg/m^2 [52]. A high BMI has also been linked to progression of preexisting glomerulonephritis (i.e., IgA nephropathy) and inherited illnesses like polycystic kidney disease and nondiabetic kidney disease [53–55].

Obesity is also a risk factor for progression to ESKD. In a population of over 300,000 adults, a higher BMI independently predicted the development of ESKD even after adjusting for baseline blood pressure, the presence of diabetes, and other risk factors [56]. Compared to individuals with normal BMI the adjusted relative risk for ESKD was 1.87 for overweight individuals, 3.57 for a BMI of 30–34.9 kg/m^2, 6.12 for a BMI of 35–39.9 kg/m^2, and 7.07 for a BMI $\geq$ 40 kg/m^2. This relationship holds in younger individuals as well. A retrospective study of 1.2 million Israeli adolescents followed over an average of 25 years reported that being overweight or obesity independently associated with the development of ESKD. The relationship was notably pronounced for diabetic ESKD, with a hazard ratio of ~39 for youths in the >95th BMI percentiles [57]. Obesity has even been linked to a more rapid decline in residual kidney function at time of initiation of dialysis [58] and a family history of end-stage renal disease (ESRD) [59]. Whether the latter risk is due to environmental or genetic factors is unknown.

The impact of obesity on kidney health is of great consequence. In 2015 CKD was the second leading cause of high BMI-associated disability-adjusted life years (5.5 million) after cardiovascular disease [60]. That same year CKD also accounted for about 188,000 high BMI-related deaths.

The obesity paradox

In contrast to its adverse association with kidney function, BMI has been shown in numerous observational studies to have a protective association with survival (Fig. 40.1). This association is known as the obesity paradox and is especially notable in patients on hemodialysis, though a similar relationship has also been seen in other chronic disease populations [61–63].

There are several possible explanations for the obesity paradox. These include increased cardiovascular stability, greater resistance against infections, and better overall fitness and less hypotension seen in patients with higher versus lower BMI [63]. Because BMI does not distinguish between different body compartments or type of fat distribution, studies have tried to tease out their relationship to outcomes. In general, they report that increased fat (when it does not reflect central obesity) and especially increased muscle mass are associated with higher survival [12,64–66].

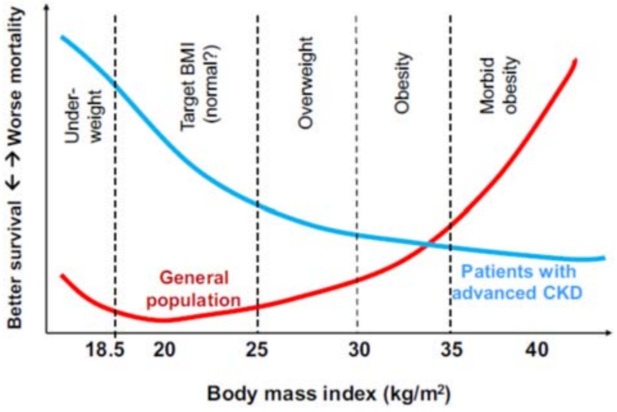

FIGURE 40.1 Reverse association of body mass index and survival in patients with advanced chronic kidney disease as compared to the general population. Source: *Reprinted with permission from* [63].

However, the obesity paradox of CKD has been criticized for its methodological limitations [67]. Detractors have raised concerns about multiple residual confounders and biases while supporters point to the general consistency of the observational data throughout numerous studies [63,67]. Regardless of the ultimate validity of the obesity paradox theory, it does not directly inform the clinically pertinent question of whether patients with CKD and obesity would benefit from weight reduction therapy. One observational study found a relationship between greater weight loss after initiating hemodialysis and higher mortality but the weight lost may have been unintentional, thus representing underlying pathology [68]. On the other hand, a recent study observed that *intentional* weight reduction via bariatric surgery in very obese individuals with ESRD improved survival [69]. The mortality rate in the surgery cohort at 5 years was 31% lower (0.69, 95% confidence interval 0.60–0.78) compared to a matched cohort getting usual care. This finding appears to challenge the concept underlying the obesity paradox that excess weight in patients with CKD is beneficial for outcomes.

Obesity-related kidney disease

Apart from its role in promoting intermediate disease states like diabetes and hypertension, the two most common causes of ESRD [70], obesity directly damages the kidneys through putative mechanisms such as intraglomerular hypertension, podocyte depletion, reduced nephron endowment, upregulation of the sympathetic system and renin–angiotensin–aldosterone axis, obstructive sleep apnea, insulin resistance, lipotoxicity, fat infiltration, and adipokines. A distinct entity called obesity-related glomerulopathy (ORG) is characterized by proteinuria, glomerulomegaly, and in certain circumstances glomerulosclerosis and progression of CKD [71]. The true incidence and prevalence of ORG is not known because of different regional biopsy patterns and the fact that the clinical manifestations of ORG may be quite subtle. Clinical differences between ORG-related and primary focal segmental glomerulosclerosis (FSGS) are shown in Table 40.3.

Obesity-related intraglomerular hypertension is a result of several factors, including increased proximal tubular sodium uptake possibly from increased sympathetic activity [72], greater circulating angiotensin II (Ang II) [73], or other mechanisms. The reduced sodium load downstream deactivates tubuloglomerular feedback [74] leading to afferent arteriolar dilation, an increased filtration fraction, and direct transmission of higher (and ultimately detrimental) systemic blood pressures to the glomerulus [75]. Compounding this is a volume expanded state induced by increased proximal tubular sodium uptake [73,75–77]. A higher GFR and higher filtration fraction increase oncotic pressure in the peritubular capillaries that in turn also promotes proximal sodium absorption [73]. Taken together, the process involves a vicious cycle that promotes structural damage within the glomerulus. The process is shown in Fig. 40.2.

Podocytes help maintain the glomerular basement membrane filtration mechanism and have limited capacity for cell division and replacement [78]. Increased caloric intake stimulates glomerular hypertrophy likely through the mammalian target of rapamycin pathway [79,80]. This causes a maladaptive response in which podocytes attempt but are ultimately unable to sufficiently hypertrophy to maintain the filtration barrier. The result is denuded areas on the capillary loops that are a nidus for segmental glomerulosclerosis. This theory is supported by evidence showing that in humans increased glomerular volume associates with reduced podocyte density and greater foot process width that are risk factors for proteinuria [81]. Ang II, aldosterone, plasminogen activator inhibitor-1, and hyperlipidemia are all upregulated in obesity while adiponectin is downregulated. All these factors have also been hypothesized to contribute to podocyte depletion [82–86].

The reason why only certain obese individuals develop ORG may be related to nephron endowment. Individuals born with reduced nephron mass and relatively low nephron numbers, such as is the case of small-for-gestational age or preterm births, are susceptible to developing hypertension and in certain circumstances kidney disease [87]. Similarly,

TABLE 40.3 Clinical and pathologic differences between obesity-related glomerulopathy (ORG)-related and primary focal segmental glomerulosclerosis (FSGS).

Characteristic	ORG-related FSGS	Primary FSGS
Age at presentation	Most common in middle-aged adults (mean age 37–46 years) but may be present in children and older adults	Most common in children and young adults
Clinical presentation	Slowly progressive proteinuria	Sudden onset of proteinuria with full nephrotic syndrome in most cases
Proteinuria and serum albumin	• Subnephrotic proteinuria in 52%–90% of patients • Normal serum albumin levels	• Nephrotic-range proteinuria in most patients • Hypoalbuminemia is common
Full nephrotic syndrome[a]	Unusual (<5% of patients) even in patients with massive proteinuria	Common
Clinical course	• Slower progression than primary FSGS • Renal survival 75% at 5 years and 50% at 10 years	• Faster progression than ORG-related FSGS • Renal survival 50% at 5 years and 25% at 10 years
Glomeruli with FSGS lesions	Fewer than in primary FSGS (mean 12% of glomeruli)	More frequent than in ORG-related FSGS (mean 39% of glomeruli)
FSGS variants	Perihilar variant more common	Note otherwise specified, tip, and collapsing variants more common
Glomerulomegaly	Defining feature of ORG (100% of cases)	Variable (10% of cases)
Foot process effacement	Usually <50% glomerular surface area	Usually >50% glomerular surface area

[a] *Hypoalbuminemia, hyperlipidemia, and edema.*

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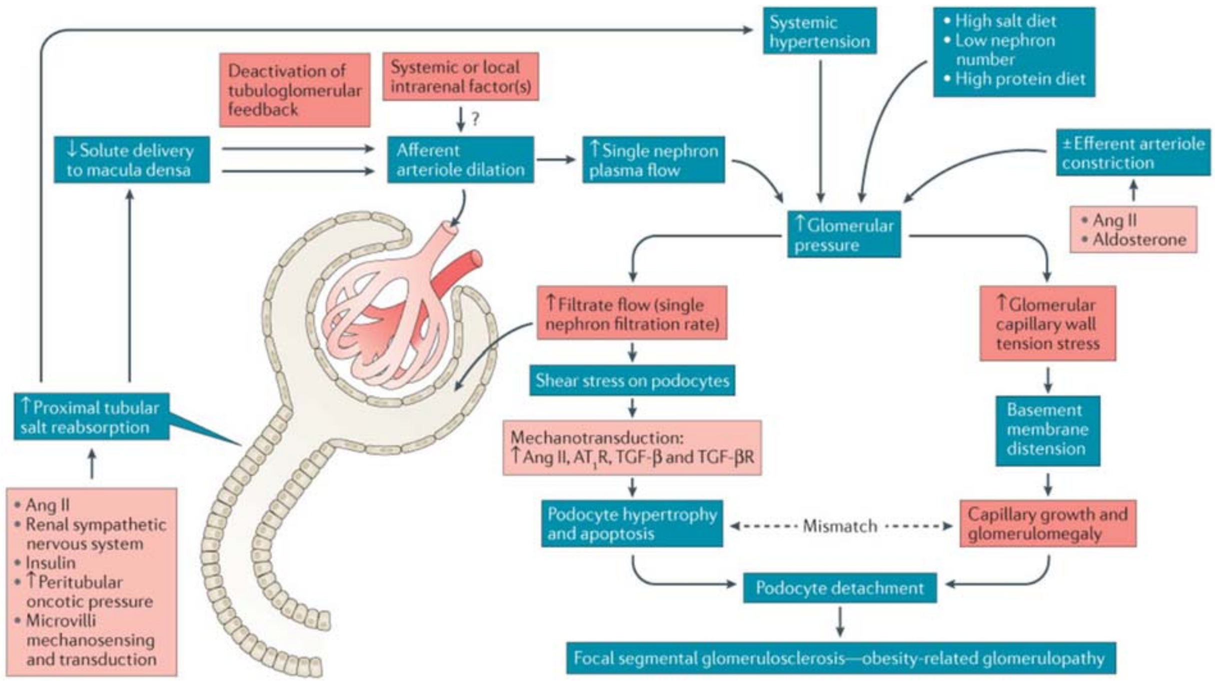
Systemic hypertension
• High salt diet
• Low nephron number
• High protein diet
Deactivation of tubuloglomerular feedback
Systemic or local intrarenal factor(s)
?
↓Solute delivery to macula densa
Afferent arteriole dilation
↑Single nephron plasma flow
±Efferent arteriole constriction
• Ang II
• Aldosterone
↑Glomerular pressure
↑Filtrate flow (single nephron filtration rate)
↑Glomerular capillary wall tension stress
Shear stress on podocytes
Basement membrane distension
Mechanotransduction: ↑Ang II, AT1R, TGF-β and TGF-βR
↑Proximal tubular salt reabsorption
• Ang II
• Renal sympathetic nervous system
• Insulin
• ↑Peritubular oncotic pressure
• Microvilli mechanosensing and transduction
Podocyte hypertrophy and apoptosis
Mismatch
Capillary growth and glomerulomegaly
Podocyte detachment
Focal segmental glomerulosclerosis—obesity-related glomerulopathy

FIGURE 40.2 Hemodynamic alterations in obesity. Primary dilatation of the afferent arteriole and variable constriction of the efferent arteriole via activation of Ang II and aldosterone contribute to increases in single-nephron plasma flow, glomerular intracapillary hydrostatic pressure, and filtration rate. The major driver of afferent arteriolar dilatation is unknown, but deactivation of tubuloglomerular feedback via increased proximal tubular salt reabsorption and decreased delivery to the macula densa likely has a role. A host of factors, including Ang II, the renal sympathetic nervous system, insulin, an increase in postglomerular oncotic pressure due to increased filtration fraction, and mechanosensors of tubular flow rates, mediate the increased tubular reabsorption of sodium. The increase in filtrate flow (single-nephron filtration rate) in turn promotes glomerular capillary wall stretch tension, glomerulomegaly, and maladaptive podocyte stress leading to obesity-related glomerulopathy and focal segmental glomerulosclerosis. *Ang II*, Angiotensin II; *AT_1R*, type 1 angiotensin II receptor; *TGF-ß*; TGF-ßR, TGF-ß receptor. Source: *Reprinted with permission Ladhani, M, et al., Obesity and the risk of cardiovascular and all-cause mortality in chronic kidney disease: a systematic review and meta-analysis. Nephrol Dial Transpl 2016;32(3):439–49.*

the presence of obesity in persons with reduced nephron mass may lead to kidney damage [88]. One line of evidence that reduced nephron endowment or mass is the key factor determining development of ORG are histological studies showing that patients with ORG have lower glomerular and podocyte density and increased glomerular size compared with controls [81,89]. However, whether fewer glomeruli are a cause or consequence of ORG has not yet been definitively established.

The deleterious renal effects of renin–aldosterone axis upregulation such as seen in obesity [90] are well established and explain why inhibitors of this axis may be effective treatments for kidney disease in overweight patients [91,92], though not all evidence supports this strategy [93]. Experimental studies in animals and observational trials in humans find that Ang II and aldosterone play an important role in obesity-related hypertension and kidney disease [94–96]. Possible mechanisms include sympathetic nerve stimulation, insulin resistance, and hemodynamic alterations that promote renal cellular toxicity and fibrosis [96,97].

Obstructive sleep apnea, elevated-circulating leptin levels, and hyperinsulinemia have all been postulated to increase sympathetic nerve activity in obesity with resultant sodium retention [72,98]. In a dog model, kidney denervation prevented a rise in blood pressure and greatly lowered sodium retention though renal hemodynamics remain unchanged [98].

In addition to increased sympathetic activity, obstructive sleep apnea has been linked to obesity-related FSGS [99] and proteinuria [100–102] though the association is not unequivocal [103]. One report described how initiation of BiPAP ventilation preceded the disappearance of nephrotic-range proteinuria in a patient with obesity-hypoventilation syndrome and biopsy-proven FSGS [102]. A postulated mechanism involves regression of pulmonary hypertension-associated abnormalities in renal blood flow and sympathetic nerve activity.

The importance of insulin-sensitivity to proper glomerular function was highlighted using a murine model in which insulin receptors were deleted from podocytes [104]. Over time the mice developed albuminuria and glomerulosclerosis. In humans the link between insulin resistance, a hallmark of obesity and the metabolic syndrome, and kidney disease is primarily based on associative data [105,106]. Indeed, it is difficult to tease out the specific effects of insulin resistance from other abnormalities that cluster in patients with the metabolic syndrome.

Excess lipids accumulating in mesangial cells, podocytes, and tubular cells can damage cellular structural integrity and lead to maladaptive metabolic changes that contribute to kidney disease [107]. Targeting pathways involved in lipid metabolism have been shown in animal studies to limit lipid-related injury [71].

Fat accumulation in renal sinuses has been linked to kidney disease [108,109] perhaps through direct compression of renal parenchyma resulting in increased renal interstitial pressure, sodium reabsorption, and other adverse effects. Notably, weight loss has been shown to reduce renal sinus fat in persons without CKD [110].

Fat cells are now understood to secrete a range of biologically active molecules, some of which have been investigated for possible deleterious effects on the kidney [111]. Two of the most prominent are leptin and adiponectin. Leptin was first studied for its role in appetite and metabolic regulation but is now also understood to mediate the obesity-associated increase in blood pressure [112]. In addition, cell and animal models exposed to leptin develop glomerular endothelial cell proliferation, increased TGF-β1 secretion, and glomerulosclerosis and collagen deposition within the glomerulus [113]. Adiponectin has insulin-sensitizing effects and its levels are inversely associated with adipose mass [114]. Mice that cannot express adiponectin manifest increased levels of albuminuria and podocyte foot process fusion while treatment with adiponectin reverses these effects [86]. In observational studies adiponectin is inversely correlated with proteinuria [86,115]. A direct effect of adiponectin on podocytes is postulated to occur at least in part through stimulation of the AMP-activated protein kinase pathway that inhibits reactive oxygen species [116]. Whether adipokines truly mediate kidney disease or are simply an epiphenomenon remains open to debate as the available evidence is primarily based on in vitro or animal models that may not reflect human physiology. In addition, the fact that some adipokines are filtered and reabsorbed in the nephron makes it challenging to differentiate their biologic effects from those related to changes in GFR.

Management of obesity-related kidney disease

Nonweight loss strategies

Blockade of the renin–angiotensin–aldosterone (RAAS) axis with resultant lowering of intraglomerular pressure offers a potentially effective strategy for renoprotection. A retrospective study in 17 patients with nephrotic-range proteinuria suggested that treatment with the angiotensin-converting enzyme (ACE) inhibitor captopril had the equivalent effect of weight loss in reducing proteinuria [91]. A post hoc analysis of the Ramipril Efficacy in Nephropathy trial, which randomized 352 patients with nondiabetic nephropathy to either the ACE inhibitor ramipril or matched placebo, reported that ramipril reduced the cumulative incidence of ESKD in patients who were obese and to a lesser extent overweight but had no effect in persons with normal BMI [92]. The antiproteinuric effect of ramipril also increased with higher BMI. However, a retrospective database analysis of 219,701 obese primary care patients did not find RAAS blocker use effective in preventing a 50% reduction in eGFR, ESKD, or death, even in the tiny fraction of patients with proteinuric CKD [93]. Nevertheless, despite these mixed findings, it seems reasonable given their study design limitations to consider the use of RAAS inhibitors in obese patients with CKD, particularly when they have proteinuria.

Weight loss strategies

A standard strategy when treating CKD is to target each risk factor individually. An alternative strategy is to target them collectively by addressing the root cause—namely, obesity—through a weight reduction intervention. A large portion of obese patients across the spectrum of CKD are not only interested in losing weight but attempt to do so [117,118]. This is noteworthy because intentional weight reduction if obtainable would appear to be the most direct and intuitive strategy to help combat the adverse kidney effects of obesity. Weight reduction treatment options include anorectic medications, lifestyle and dietary interventions, and bariatric (a.k.a. metabolic surgery).

Medications

The use of the five medications currently approved by the Food and Drug Administration (FDA) for weight loss is limited by dosing and other toxicities in persons with CKD, especially in advanced stages (see Table 40.4).

Nevertheless, early evidence for two of the five approved drugs is suggestive of renoprotective benefits. In a secondary analysis of 9340 obese patients with type 2 diabetes and high cardiovascular risk, the glucagon-like peptide 1 (GLP-1) analog liraglutide reduced the composite renal outcome by 22% over

TABLE 40.4 Long-term pharmacologic treatment for weight loss approved in the United States.

Drug (brand name)	Mechanism of action	Common adverse effects	Kidney-related precautions	Dosing adjustments	
				Stages 3–5 CKD	**ESKD**
Orlistat (Xenical, Alli)	Lipase inhibitor thus inhibiting absorption	Fecal incontinence, oily spotting, fat-soluble vitamin deficiency	Reports of acute kidney injury possibly from oxalate nephropathy	None	None
Lorcaserin (Belviq)	Serotonin agonist, anorexic	Headache, dizziness, fatigue, dry mouth, cough	Excreted primarily via the urine	Stage 3: Use with caution Stages 4–5: not recommended	Avoid use
Phentermine/ Topiramate (Qsymia)	Sympathomimetic, anorexic	Dry mouth, constipation, paresthesia, proximal (type 2) renal tubular acidosis, calcium kidney stones	Excreted primarily via the urine	Stage 3: lower maximum dose Stages 4–5: avoid use	Avoid use
Bupropion–naltrexone (Contrave)	Inhibits norepinephrine/ dopamine uptake, opioid antagonist	Nausea, constipation, dry mouth, dizziness, transient increase in blood pressure, contraindicated in uncontrolled hypertension	Excreted primarily via the urine	Low maximum dose	Avoid use
Liraglutide (Saxenda)	Glucagon-like peptide-1 agonist	Nausea/vomiting, diarrhea, anorexia	None	None (limited data—use with caution)	None (limited data—use with caution)

CKD, Chronic kidney disease; *ESKD*, end-stage kidney disease.

Reprinted with permission from Kramer, H, et al., Obesity management in adults with CKD. Am J Kidney Dis 2009;53(1): 151–65.

4 years compared to placebo [119]. In a similar exploratory study of 9901 participants, the GLP-1 receptor agonist dulaglutide improved the composite renal endpoint by 15% [120]. A third trial in 12,000 overweight or obese patients with high cardiovascular risk reported that compared to placebo the serotonin agonist lorcaserin lowered the primary renal outcome by 13% over 3.5 years [121]. Both drugs achieved about a relatively modest 3- to 4-kg weight loss differential compared to placebo over the study period. While promising, caution is advised when interpreting these results as they were based on prespecified secondary outcomes so are only hypothesis-generating. Additionally, they included relatively few individuals with established CKD and harder outcomes (e.g., doubling of serum creatinine, ESKD, kidney transplant, death) were few in number and not different between the two arms. In fact, the positive results reported were due mostly to albuminuria-lowering effects.

In addition to FDA-approved medications, there are additional anorectic drugs with possible renoprotective effects. Chief among these is the new medication class of sodium–glucose cotransporter 2 (SGLT2) inhibitors, a promising new class of diabetes medications that induce about a 2- to 3-kg weight loss, and prespecified secondary analyses have reported major reductions in kidney risk [122,123]. However, the Effects of Canagliflozin on Renal and Cardiovascular Outcomes in Participants with Diabetic Nephropathy trial, which randomized 4401 patients with type 2 diabetes and albuminuric CKD to the SGLT2 inhibitor canagliflozin or placebo, found only an 0.8-kg average lower weight in the active arm after a median follow-up of 2.6 years [123].

Medical and lifestyle interventions

Dietary restriction, lifestyle interventions, and a combination of these in conjunction with anorectic medications have also been prospectively studied in patients with or at risk for CKD [124–128] though what is currently lacking are randomized studies that directly measure the trajectory of GFR and endpoints like ESKD, transplant, hospitalization, or mortality. Of all the available studies, one stands out for its study design, statistical power, and length of follow-up [125]. The Action for Health in Diabetes (Look AHEAD) trial randomized 5145 individuals who were overweight or obese with type 2 diabetes to an intensive lifestyle intervention or standard support and monitored weight loss over time. The intensive lifestyle intervention involved reduced caloric intake (goal 1200–1800 kcal/d) and increased physical activity (at least 175 minutes of moderate exercise weekly) while the standard support group focused on diet, exercise, and social support. Over a median 8-year follow-up period, the intensive lifestyle intervention group lost 4 more kg than the standard treatment arm and also had minor improvements in blood pressure and hemoglobin A1c levels. A substudy of the trial examining kidney-related outcomes found a reduction in very-high-risk CKD in the intervention arm [hazard ratio 0.69 (0.55−0.87)] (see Fig. 40.3) as well as statistically significant improvements in reaching eGFR < 45 mL/min/1.73 m^2 [0.79 (0.66−0.96)] and a trend toward reduced albuminuria of >300 mg/g [0.81 (0.66−1.01)].

There was no difference in risk of requiring renal replacement though very few such events occurred. While this study offers hope that even modest weight loss through lifestyle or dietary interventions may slow the development and progression of CKD, it does have notable limitations. These include very few patients with preexisting CKD, few hard outcomes achieved, and its design as a secondary analysis, thus necessitating confirmation in future studies.

Surgical weight loss

Bariatric (also known as metabolic) surgery involves an alternative approach to weight loss that is more effective and sustained overall than dietary or lifestyle interventions. It also is superior in improving major risk factors for CKD and the metabolic syndrome such as excess adiposity, diabetes, insulin resistance and hyperinsulinemia, hypertension, and intraglomerular hypertension. In one recent randomized controlled trial, two different modalities of bariatric surgery induced a larger, faster, and more sustained reduction in the BMI, hemoglobin A1c, and fasting plasma glucose after 5 years of

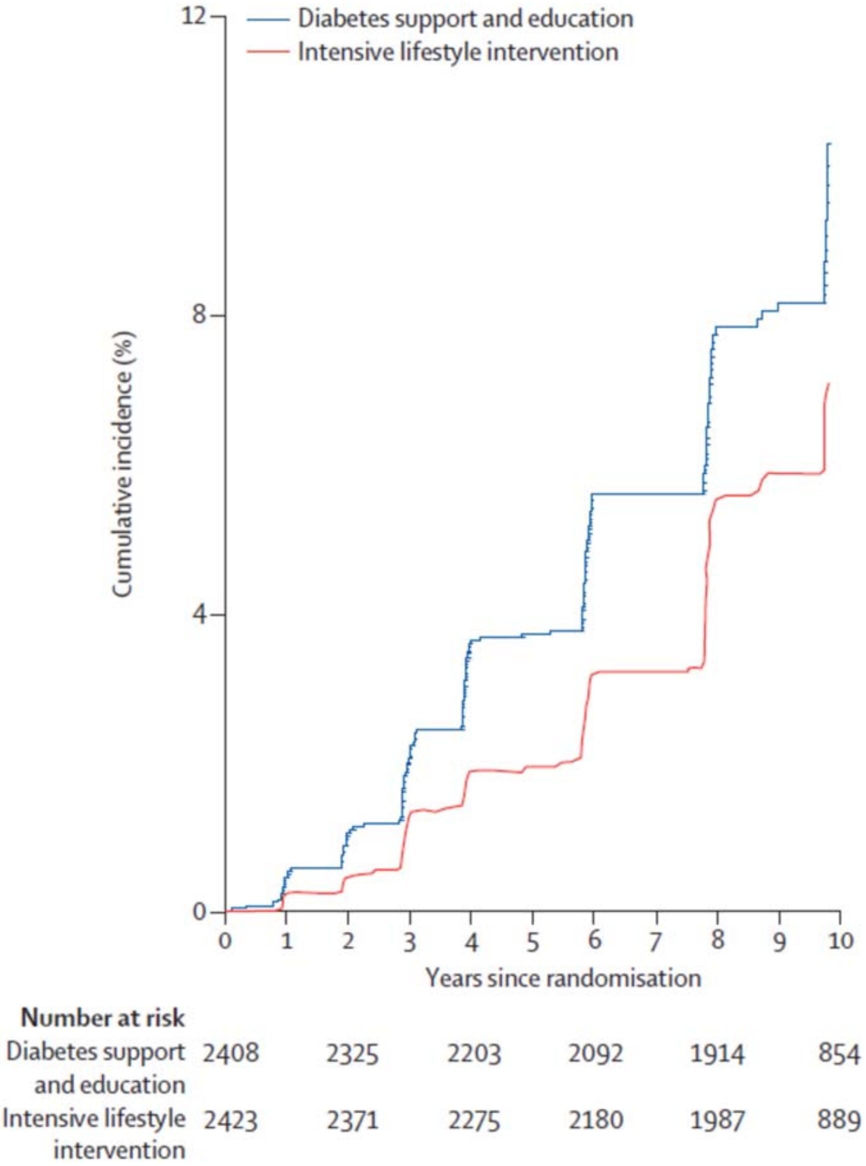

FIGURE 40.3 Cumulative incidence of very-high-risk chronic kidney disease. Too few observations were available beyond year 10 for reliable estimates. Source: *Reprinted with permission from Look AHEAD Research Group. Effect of a long-term behavioural weight loss intervention on nephropathy in overweight or obese adults with type 2 diabetes: a secondary analysis of the Look AHEAD randomised clinical trial. Lancet Diabetes Endocrinol 2014;2(10):801−9.*

follow-up compared to intensive medical therapy [129]. Specifically, 23% and 29% of patients in the two bariatric surgery arms, respectively, achieved a hemoglobin A1c of ≤6% versus only 5% in the medical therapy arm.

In a separate randomized trial designed specifically to measure the effect of bariatric surgery on blood pressure control, Roux-en-Y gastric bypass (RYGB) dramatically lowered the need for antihypertensive medications and/or induced remission of hypertension by 12 months compared to medical therapy [130]. In nonrandomized studies, bariatric surgery is associated with improvements with additional risk factors for CKD, including glomerular hyperfiltration [23], albuminuria [131], pulmonary hypertension, right ventricular size and function [132], obstructive sleep apnea [133], and left ventricular hypertrophy [134].

The first study to analyze the effect of bariatric surgery on kidney disease was performed by Chang et al. who compared a cohort of 985 adults with normal mean baseline kidney function with 985 propensity-matched controls. Bariatric surgery was associated with a 58% [hazard ratio 0.42 (0.32, 0.55)] lower risk of decline in eGFR and a 57% lower risk of doubling in serum creatinine or ESKD [0.43 (0.26, 0.71)] (Fig. 40.4) [135]. However, the number of events was few and the majority of persons defined as having ESKD were actually not on dialysis. A more recent study also reported a reduction in the incidence of ESKD, but similar to the Chang et al. study, the outcome definition was liberalized to include patients not yet on dialysis and the actual events were few in number [136].

Additional reports have found benefits of bariatric surgery in a population with baseline CKD and using prognostic risk for CKD as the major outcome [137,138]. Several studies have also examined this issue in patients with type 2 diabetes, a group that may especially benefit from the effects of bariatric surgery, and found evidence albeit observational of renoprotective effects [139–142].

Relationship between weight loss and renoprotection

Whether a direct relationship exists between the amount of weight lost and renoprotection is under debate. In a Zucker diabetic fatty rat model, RYGB was compared to equivalent weight loss by diet restriction to evaluate the effects on the kidney [143]. As compared to the ad libitum sham group both gastric bypass and diet restriction–related weight reduction approaches reduced to a similar extent the likelihood of glomerulomegaly and glomerulosclerosis, macrophage infiltration within the kidney, and urinary and parenchymal inflammatory markers. However, RYGB proved more effective in reducing proteinuria, suggesting a component of weight loss–independent benefits. This conclusion was echoed in a recent metaanalysis [144].

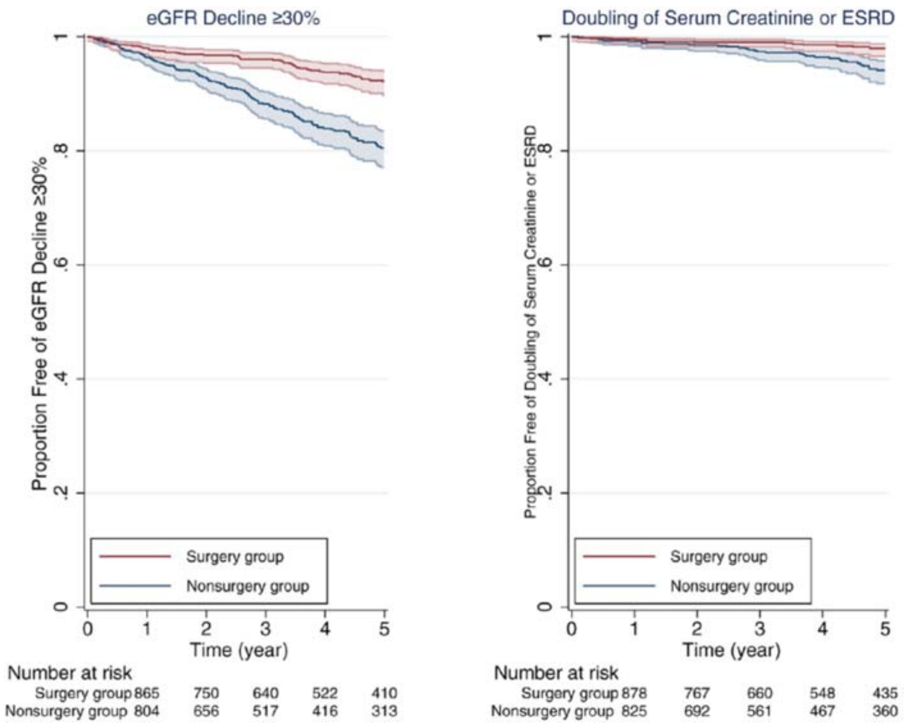

FIGURE 40.4 Kaplan–Meier curves estimating time to kidney outcomes by surgery group and control group. The eGFR decline ≥30% outcome was defined as having a follow-up outpatient eGFR ≥ 30% lower than the baseline eGFR value. ESRD was defined as eGFR < 15 mL/min/1.73 m^2 or treated ESRD per US Renal Data System registry. Shaded areas represent 95% confidence interval bounds. *eGFR*, Estimated glomerular filtration rate; *ESRD*, end-stage renal disease. Source: *Reprinted with permission from [135].*

Management of the metabolic syndrome

Treatment of the metabolic syndrome can be directed toward each individual component or the sum total. Lifestyle modification focusing on weight reduction and increased physical activity is first-line therapy for the metabolic syndrome [145]. Antidiabetic drugs such as metformin, GLP-1 agonists, dipeptidyl peptidase IV inhibitors, and SGLT2 inhibitors, statins for dyslipidemia, and RAAS blockers for hypertension can also be considered in conjunction with lifestyle changes [146].

Knowledge gaps

As described, there is growing evidence from a variety of studies to support the premise that intentional weight loss strategies lower albuminuria and improve or stabilize eGFR. Yet this literature has notable limitations in study design, participant selection, statistical power, and measurement issues that must be overcome to better define any kidney-related benefits. Of particular concern are the lack of data from randomized controlled trials and other studies that are large enough and/or include sufficient high-risk patients to offer sufficient power to measure effects on hard clinical endpoints like ESKD. Another limitation is the nearly ubiquitous use of eGFR rather than directly measured GFR for reasons that have previously been reviewed. A further concern is the lack of head-to-head studies comparing the risks and benefits of metabolic surgery versus nonsurgical weight reduction techniques.

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CHAPTER

41

Bariatric surgery and kidney disease

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Magnitude of the obesity problem

Prevalence of obesity: BMI continues to be the traditional metric by which the presence and severity of obesity are expressed. The specific calculation is weight in kilograms over height in meters squared. The definitions are detailed in Table 40.1.

Global figures for the prevalence of obesity in various patient populations utilized BMI > 30. In the United States, various databases put the incidence of obesity in adults at 30%−40% with some variation according to patient populations defined by race, gender, ethnicity, and others. The incidence of obesity among adolescents is 15%−17%, with the majority remaining obese as adults. While the prevalence of obesity remains exceedingly high, recent data indicate that the incidence is not increasing in the United States. While data are difficult to acquire in many parts of the world, obesity has been identified as a global epidemic.

Clinical manifestations: While many consider the definition in the classification of obesity by BMI to be somewhat arbitrary, the mortality risk associated with increasingly severe obesity provides the basis for declaring a BMI of >30 to represent a mortality risk with increasing mortality as BMI increases [1]. The mortality risk per BMI unit is greater in men than women with a sharp increase at BMI > 40 [1].

There are multiple comorbidities associated with increasingly severe obesity. The occurrence of multiple comorbidities complicates the estimation of the determination of the risk of obesity apart from these comorbid conditions, including risk factors for chronic kidney disease (CKD) and cardiovascular disease as outlined later.

Glucose metabolism: The prevalence of insulin resistance among people with obesity is 63% (BMI 30−34.9) [2] and may be greater for BMI > 35. Factors involved include interference with the action of insulin on glucose uptake in muscle by inflammation and free fatty acids among others. In addition to diminished glucose uptake, insulin resistance occurs secondary to failure of hyperglycemia and/or hyperinsulinemia to suppress hepatic gluconeogenesis. Prediabetes may commonly progress to diabetes. Details of the adverse clinical manifestations of diabetes are beyond the scope of this chapter. Diabetes is a well-known cause of CKD.

Cardiovascular disease: There are multiple manifestations or comorbidities of obesity that contribute to the risk of cardiovascular disease. These include but are not limited to diabetes, hypertension, dyslipidemia, and obstructive sleep apnea. In addition to atherosclerotic occlusive disease, cardiomyopathy with secondary congestive heart failure and venous thromboembolism are direct comorbidities of obesity.

Cancer: The association of multiple cancers with obesity has been identified. The relative risk (RR) of certain cancers compared to normal weight individuals includes endometrium (RR 6.3), breast (RR 2.1), gastrointestinal (GI) cancers from esophagus to rectum (RR 1.8−2.6), kidney (RR 1.7), and others. Virtually all malignant diseases, including melanoma, are associated with increased risk in people with obesity other than lung cancer, which is dominated by smoking. The incidence of the association of cancers in men is elevated, although not as much as in women. In addition to the previous cancers, cancer of the liver is increased in men (RR 4.5) [3].

Quality of life/psychological impairment: Obesity causes decreased physical functioning due to musculoskeletal disease as well as weight itself. Impaired quality of life, depression, and suicidal ideation may also develop [4,5]. Social impairment such as limited employment opportunities and other social manifestations of obesity-related bias are also highly prevalent.

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There are multiple other comorbid conditions too numerous to include in this discussion.

The incidence of these comorbidities steadily or progressively increases with the severity of obesity [6]. For example, the prevalence of each comorbidity with the possible exception of hypertension is progressively greater as the BMI rises above 40, 50, and 60 [6]. Pertinent to these data is the very high prevalence of comorbidities associated with a risk of subsequent endpoints such as cardiovascular disease and CKD. These endpoints have often not been identified among the bariatric surgery population. As a result, there is an opportunity in many of these patients to improve such outcomes through weight loss [7].

Pathogenesis of obesity

The major components of the pathogenesis of obesity are excessive energy intake and sedentary lifestyle/diminished physical activity and energy expenditure. Of these, excess energy intake is the predominant factor. While precise data are difficult to acquire, it is evident that the excessive intake is largely due to the production and promotion of high-energy foods that are appealing to a wide majority of people at low cost. For example, in the United States, the percentage of income necessary to consume excess energy is lower than for any population in history [8]. There are numerous factors that contribute to the severity of obesity in addition to the readily available food produced and marketed to meet desirable taste. Genetics is one such factor. There are definite congenital causes of obesity which lead to severe obesity among young children, although these syndromes, such as the Prader–Willi syndrome, are rare. The role of the genetics in the present obesity epidemic is much more difficult to identify with precision due to the multiple genes which may contribute to obesity and the interaction of combinations of these genes with one another as well as the environment. Observed phenomena, precise mechanisms of which have not been identified, include variable sites at which triglyceride is stored. Uptake and storage of excess energy as triglyceride by subcutaneous adipocytes is associated with lesser degrees of secondary pathology than is accumulation of lipid at pathologic sites such as liver and muscle. While the accumulation of triglyceride in hepatocytes is reversible with weight loss for the most part, steatohepatitis, leading to fibrosis, cirrhosis of the liver, and ultimate liver failure as well as hepatocellular carcinoma, is one example of the clinical manifestations of a variation in the site of accumulation of fat and related pathology. As with many conditions, the induction of variable systemic inflammation is thought to be a primary mechanism by which these comorbid conditions may occur. The mass of the accumulated fat may also be a pathogenic factor in conditions such as obstructive sleep apnea, musculoskeletal dysfunction, and disability.

Role of bariatric surgery

Two distinguishing features of weight loss after bariatric surgery are the magnitude of weight lost and its long-term maintenance [7,9,10]. Obesity is a chronic disease, and while weight may be lost with medical or lifestyle interventions, weight regain ensues in over 95% of patients, even with continued participation treatment [11]. Despite the efficacy of bariatric surgery <1% of patients for whom it is indicated actually access it. Indications for bariatric surgery last discussed in published consensus guidelines [12] agreed with previous 1991 NIH guidelines [13]. Bariatric surgery is indicated for patients with BMI > 40 or 35–39.9 kg/m^2 with high-risk comorbidities for whom medical and/or lifestyle interventions have failed to achieve or maintain adequate weight loss to improve their health. High medical-risk comorbidities include those that increase risk for cardiovascular disease and include the two most common causes of end-stage kidney disease (ESKD)—type 2 diabetes and hypertension. Other high-risk comorbidities are hyperlipidemia, sleep apnea, insulin resistance, coronary artery disease, and disabling joint disease.

Relative and absolute contraindications to bariatric surgery are preexisting illnesses which increase perioperative risk to unacceptable levels. Examples are severe-stage liver cirrhosis, undiagnosed/untreated sleep apnea, or cardiac disease, American Society of Anesthesiologists physical classification >4, and inability to tolerate general anesthesia. A patient should not be pregnant or have untreated, active cancer. Preexisting conditions that may increase the perioperative risk of surgery but do not necessarily preclude undergoing bariatric surgery are the history of venous thrombosis/pulmonary embolism, dependence on glucocorticosteroids, autoimmune disease, or previous abdominal operations. ESKD alone is not a contraindication to bariatric surgery. Most bariatric surgery programs will withhold operating if patients are current smokers, drug/alcohol abusers, or have untreated Axis I diagnoses (psychiatric diagnoses other than mental retardation or personality disorders). Appropriate cessation of unhealthy or controlled substances, or treatment to control psychiatric symptoms in these patients can reestablish suitability to undergo bariatric surgery.

Bariatric operations

The most frequently performed bariatric operations in the United States are, in decreasing order, vertical sleeve gastrectomy (58.1%), Roux-en-Y gastric bypass (gastric bypass; 18.7%), gastric band (3.4%), and biliopancreatic diversion/duodenal switch (BPD/DS; 0.6%) [14]. Worldwide frequencies share a similar volume ranking [15]. The vast majority of bariatric operations are done laparoscopically [16]. Each operation employs a method for decreasing the stomach's capacity to take in a large volume of food (Fig. 41.1). Sleeve gastrectomy, gastric bypass, and BPD/DS accomplish decreasing the stomach reservoir capacity by resection or division. The gastric band decreases stomach reservoir capacity by partitioning a small area of the proximal stomach, and by doing so, it delays delivery of food to the distal stomach. While the mechanisms of weight loss for these operations vary, caloric restriction is common to all, in part, accomplished by reducing the stomach's ability to accommodate a large volume of solid food. Physical symptoms ranging from discomfort or nausea to pain or vomiting often develop if excess volume of food is consumed. Thus learned behavior or a conditioned response to avoiding uncomfortable physical symptoms after "overeating" contributes to patients voluntarily limiting their dietary intake.

Sleeve gastrectomy, gastric bypass, and BPD/DS benefit from the hormonal changes of decreased ghrelin and increased GLP-1, at least within the first postoperative 6–12 months [17,18]. Decreased ghrelin reduces hunger and higher GLP-1 increases satiety. These hormonal changes stem from an early delivery of food to the proximal intestine. Food reaches the intestine quickly, relative to native anatomy, as either

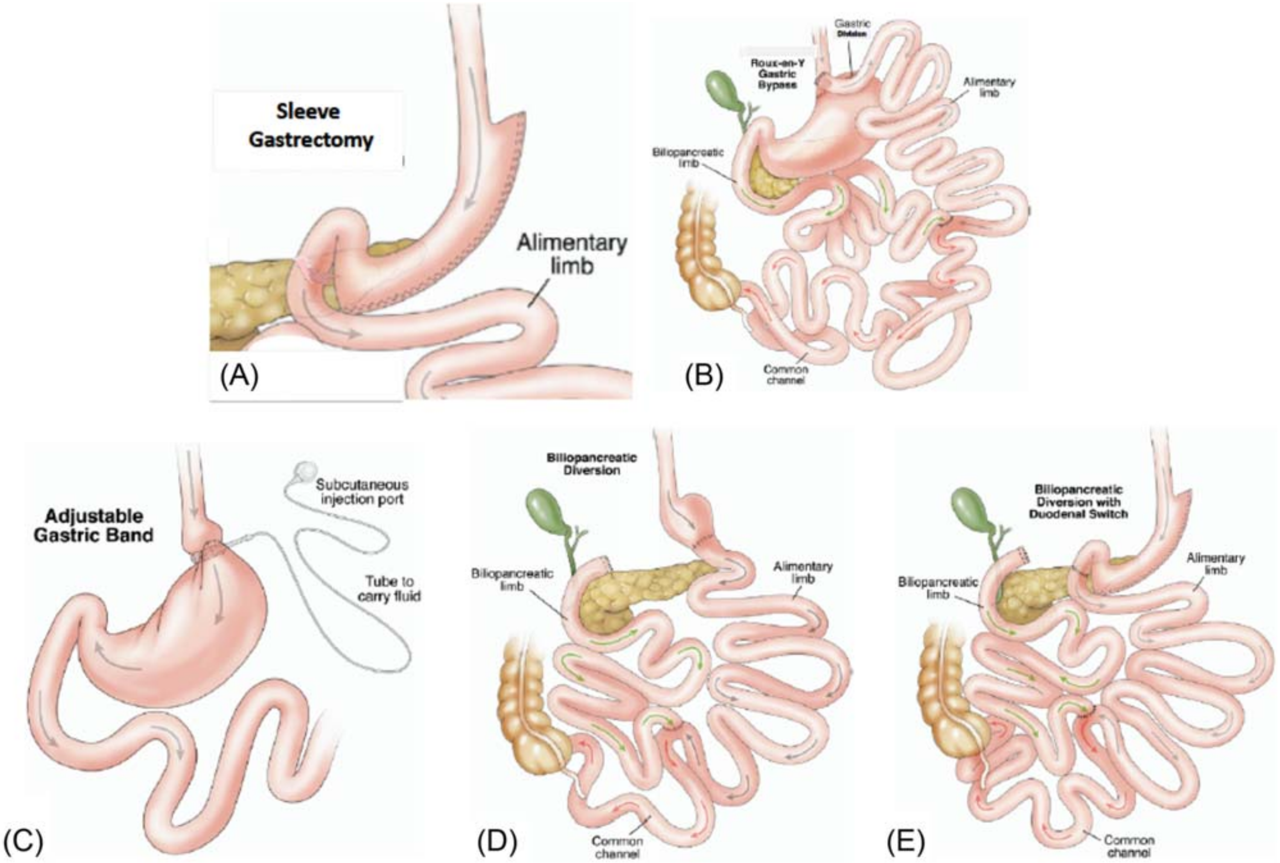
Sleeve Gastrectomy
Alimentary limb
(A)
Gastric Division
Roux-en-Y Gastric Bypass
Alimentary limb
Biliopancreatic limb
Common channel
(B)
Adjustable Gastric Band
Subcutaneous injection port
Tube to carry fluid
(C)
Biliopancreatic Diversion
Biliopancreatic limb
Alimentary limb
Common channel
(D)
Biliopancreatic Diversion with Duodenal Switch
Biliopancreatic limb
Alimentary limb
Common channel
(E)

FIGURE 41.1 Anatomy of bariatric operations. (A) Sleeve gastrectomy—the stomach is reduced by vertical resection of the greater curvature creating a narrow tube or "sleeve." (B) Roux-en-Y gastric bypass—the stomach is divided creating a proximal "pouch" of 15–30 mL. The pouch is connected to a 90- to 150-cm alimentary limb, in turn, connected to a 45- to 60-cm biliopancreatic limb. (C) Adjustable gastric band—a band with a balloon on its internal diameter circles the proximal stomach and is imbricated, creating a "pouch" of 20–30 mL. The balloon, connected to a peripheral injection port, may be tightened by saline infusion or deflated. (D) Biliopancreatic diversion—a proximal 200- to 500-mL "pouch" is created after a partial distal gastrectomy. Varying lengths of alimentary and biliopancreatic limbs are connected to create a 50- to 100-cm common channel. (E) Biliopancreatic diversion with duodenal switch—a sleeve gastrectomy replaces the partial distal gastrectomy, the pylorus is preserved and the proximal duodenum connected to the alimentary limb. Varying lengths of alimentary and biliopancreatic limbs are connected to create a 50- to 100-cm common channel.

the altered stomach empties faster (sleeve gastrectomy, BPD/DS) or as a result of intestinal rerouting and bypassing the duodenum (gastric bypass, BPD/DS). The gastric band does not benefit from hormonal changes supporting early satiety or decreased hunger [19] and results in less weight loss.

A third mechanism of weight loss after bariatric surgery was traditionally thought to be malabsorption. Malabsorption does not occur with sleeve gastrectomy or gastric band as anatomy distal to the stomach/full intestinal nutrient absorption is unchanged. In gastric bypass and BPD/DS, the proximal intestine is bypassed (approximately 45–60 cm after gastric bypass; varying greater length after BPD/DS), and there is potential for the malabsorption of micronutrients. Contrary to previous teaching, macronutrient malabsorption after gastric bypass is limited [20,21] so contributes only minimally to weight loss. BPD/DS can lead to significant macronutrient malabsorption enhancing weight loss versus other bariatric operations [20,22]. After 2 years post-BPD/DS patients are able to maintain weight loss despite eating approximately 2850 kcal/day [23].

Outcomes of bariatric surgery

Bariatric surgery versus usual-care controls with obesity results in significant, sustained weight loss and improvement or remission of obesity-related comorbidities [9,10,24]. In addition to improving CKD and type 2 diabetes, as noted in Chapter 40, Nutritional and Metabolic Management of Obesity and the Metabolic Syndrome in Patients With Chronic Kidney Disease, hypertension, hyperlipidemia, and sleep apnea also improve or go into remission [7,25–29]. Mortality from and incidence of myocardial infarction, stroke, and cancer are lowered compared to nonsurgical controls [30,31]. Health-related quality of life, 5–25 years after bariatric surgery, also shows significant improvement of physical scores by repeated self-report measure [32]. Mental health outcomes in these same studies have, however, been inconsistent.

Comorbidity resolution after bariatric surgery results from weight loss and may vary in the amount required for the improvement of individual comorbidities. Either a direct relationship between comorbidity improvement and weight loss exists (type 2 diabetes) [33] or a threshold weight-loss effect is required (sleep apnea) [27]. It is important to note that, similar to other medical treatments, there is a variation in weight-loss response to certain bariatric operations. The variation in weight loss is greater for sleeve gastrectomy and gastric band versus gastric bypass (Fig. 41.2) [7,26]. Despite less weight loss in lower treatment responders, weight-loss maintenance is still robust 5–7 years after surgery.

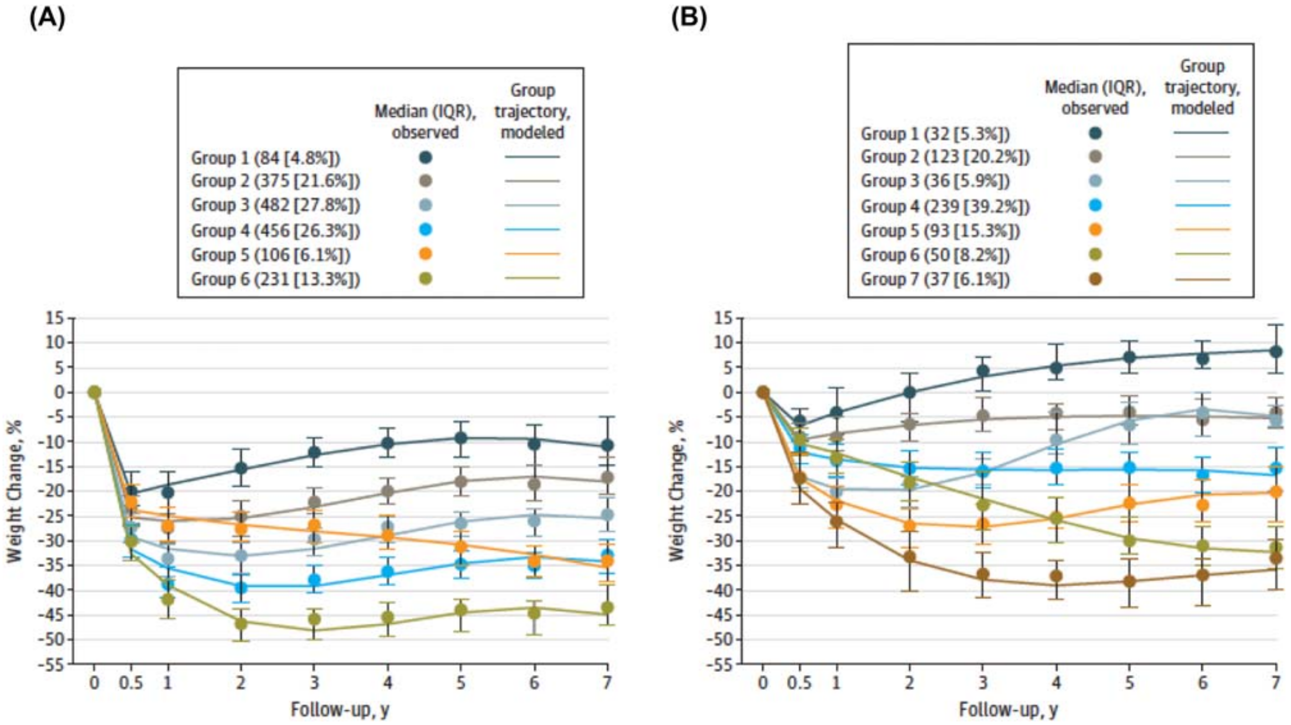

FIGURE 41.2 Percentage of weight change trajectory groups following bariatric surgery: (A) Roux-en-Y gastric bypass and (B) laparoscopic adjustable gastric band. Lines indicate modeled group trajectories, data markers, and median values; bars, IQR of observed data. Negative value indicates weight loss. *IQR*, Interquartile range.

Complications of bariatric surgery

While bariatric surgery is considered a safe elective operation, it is not without complications. Most bariatric programs are accredited by the American College of Surgeons and subscribe to reporting of outcomes to a national database for quality outcome assurance. Morbidity and mortality are classified as early—within 30 days of operation, or late—> 30 days after operation. Mortality, both early and up to 1 year, is low, <0.5% for all laparoscopic bariatric operations. Complication rates within 30 days are those common to all abdominal operations: bleeding (2%), venous thromboembolism (<0.5%), wound infection (1%–2%), obstruction (<1%), reoperation (<6%), and anastomotic leak (<1%) [34–36]. Though more common early (<20%) [36], nausea, vomiting, and dehydration may also occur late leading to malnutrition if chronic. Dumping, usually seen only after gastric bypass, occurs infrequently (<5%) and often resolves over time or with dietary limiting of simple carbohydrates. Perioperative complications vary by particular operation with gastric band being the least, followed by sleeve gastrectomy, gastric bypass, and BPD/DS. Complications usually seen within 30 days may also occur late, though when occurring late, do so with diminished frequency.

Late complications include reoperations for internal hernia, gastroesophageal reflux disease refractory to medical care, stricture causing obstruction, hypoglycemia refractory to dietary manipulations, malnutrition, treatment failure, and marginal, perforated or bleeding ulcer [7,25,26,37]. Few studies following patients for a minimum of 2 years report long-term complications (<3%), and fewer report them as a primary outcome [37]. Comprehensive long-term complication rates are evolving. Nutritional deficiencies and nephrolithiasis are more common after gastric bypass or BPD/DS [25,37]. Complications of postsurgical substance abuse, including alcohol (preoperative prevalence 10%, postoperative prevalence as high as 35%) [38], may occur at any time and require long-term surveillance for discovery and treatment.

Postbariatric surgery dietary management

The primary objective of bariatric surgery is to accomplish weight loss. Most of the secondary manifestations, including comorbidities, improve or resolve as a result of weight loss. The traditional construct of bariatric surgical procedures, as well as medical weight loss interventions, is that the weight loss is achieved by a reduction in nutrient intake and increased physical activity. Detailed studies of physical activity following bariatric surgery, however, have not demonstrated increased physical activity in this population on average [39]. Thus decreased intake is the predominant mechanism by which weight loss is achieved [21].

Malabsorption has long been presumed to be an important component of the negative energy balance and weight loss following gastric bypass, BPD/DS, and possibly sleeve gastrectomy. For example, adding a degree of intended malabsorption is the intent of the distal gastric bypass in which a more distal connection of the jejunum (150 cm) is performed. Detailed study of the contribution of malabsorption of this operative procedure to the reduction in net energy absorption utilizing sophisticated isotopic methodology showed that the malabsorption of combustible energy represented approximately 6% of the total reduction at 5 months and 11% of the total at 14 months [21]. It is, therefore, clear that careful attention to nutrient intake is of primary importance following bariatric surgical procedures. By 4 weeks postoperative the patients are generally ready to move toward a solid food diet from the early postoperative liquid diet. The general recommendations regarding nutrient management following bariatric surgery are detailed by Mechanick et al. as the guidelines established by the American Association for Clinical Endocrinologists, the Obesity Society, and the American Society for Metabolic and Bariatric Surgery [40].

Carbohydrates: Carbohydrate intake is reduced secondary to the mechanism described earlier as well as in some patients learning behavior change due to symptoms of “gastric dumping.” A component of this sensation is the rapid entry of free glucose/sugars into the jejunum where rapid absorption occurs leading to very rapid rise in plasma glucose followed by a rapid fall secondary to exaggerated insulin secretion. Despite these phenomena, carbohydrate intake generally represents approximately 50% of energy intake. Variable energy intake presumably accounts for the great majority of the wide variation in weight loss which follows bariatric surgery [7]. Approximate median or mean weight loss by the first year after bariatric surgery is gastric bypass, 27%–33% [29,41–43]; gastric band, 12%–18% [41,43]; sleeve gastrectomy, 27% [29]; and BPD/DS, 45% [42].

Fat: Fat consumption is regularly reduced similar to the reduction in carbohydrate intake leading to enhanced weight loss. Fat malabsorption contributes little to the negative energy balance. Micronutrient malabsorption as well as increased absorption of oxalate may be associated with malabsorption of lipids.

Protein: Diminished protein intake occurs largely as the result of a total reduction in nutrient intake in early months following bariatric surgery. Rapid weight loss, including the weight loss following bariatric surgery, results in the loss of lean body mass (predominantly muscle) of 10%−20% [71] [45]. This loss of lean body mass can be minimized with increased protein intake up to as much as 2.5 g protein/kg/d [46], but consumption of this amount of protein is not feasible following bariatric surgery. In addition, it is not possible to consume high-protein foods sufficiently to provide such high-protein intake without creating excess energy intake and thereby minimizing weight loss. Thus recommendations for protein intake are in the range of 0.8−1.2 g protein/kg/d [40]. Protein supplementation with high-quality protein is commonly recommended. Despite the supplementation the loss of lean body mass is approximately 10%−20% as noted earlier. Protein intake of 60−80 g/d is generally recommended. The supplementation of protein intake with essential amino acids has been shown to stimulate muscle protein synthesis in clinical trials, although none has involved bariatric surgical patients [47,48]. Manifestations of insufficient protein intake commonly seen include alopecia, anemia, and possibly low serum albumin.

Micronutrients: Micronutrient deficiency may occur due to both diminished intake and malabsorption. Malabsorption of micronutrients may occur and be clinically significant despite the minimal malabsorption of macronutrients. It should be noted that any procedure designed to increase malabsorption to enhance weight loss may or may not accomplish this goal but is regularly associated with the malabsorption of micronutrients which can be problematic.

Calcium and phosphorus: Diminished bone mineralization has been demonstrated by imaging [49]. Markers of metabolic bone disease have also been demonstrated to be increased. A degree of malabsorption of calcium, vitamin D, and phosphorus may occur. Thus increased supplementation is routinely recommended, including vitamin D in higher doses than recommended for general prophylaxis. Doses as much as 50,000 unit/d of vitamin D2 or D3 may be required [40].

Iron: Iron-deficiency anemia may occur in the absence of evidence of blood loss due to diminished intake and malabsorption. Thus supplementation is routinely recommended and intermittent IV iron supplementation may be required in addition to oral.

Vitamin B12: Deficiency of vitamin B12 due to the 90 + % exclusion of the stomach may occur. Oral supplementation of crystalline vitamin B12 at a dosage of 1000 μg daily is generally sufficient to maintain a vitamin B12 status. Parenteral B12 supplementation can be done intermittently as needed.

Thiamine: Thiamine supplementation should be included in the routine multivitamin and mineral supplementation. Thiamine deficiency may be exaggerated by protracted vomiting and/or alcohol intake. Manifestations of thiamine intake can be devastating due to central as well as peripheral neuropathy. Suspected thiamine deficiency is treated with intravenous thiamine prior to the provision of glucose-containing intravenous fluids.

Copper: Copper supplementation is also included in the routine multivitamin/mineral preparation. Copper deficiency is manifested as anemia, neutropenia, and possible myeloneuropathy. If identified, intermittent IV copper supplementation may be required in addition to oral copper.

Nutrition management of postbariatric surgery patients with CKD: The extent or stage of CKD is a primary determinant of the nutritional recommendations in patients with CKD. The National Kidney Foundation clinical practice guideline for nutrition in CKD "2020 update" has recently been published by the Kidney Disease Outcomes Quality Initiative/Academy of Nutrition and Dietetics (http://www.kdoqi.org). These guidelines must be considered in conjunction with the postbariatric surgery guidelines as specific nutrient considerations occur in both clinical situations and may differ somewhat.

Protein intake: As noted earlier, deficient protein intake is relatively common following bariatric surgical procedures leading to a substantial decrease of lean body/muscle mass, alopecia, anemia, and low serum albumin. Thus protein intake higher than 0.8 g/kg/d may be recommended, although actual protein intake is generally substantially less than recommended. This leads to a recommendation of 60−80 g protein/d. The recommended protein intake in the presence of CKD is 0.55−0.60 g/kg/d (http://www.kdoqi.org). Further reductions of protein intake may be recommended in CKD patients. The addition of ketoacids or essential amino acid supplementation may also be beneficial [47,50]. Thus in bariatric surgical patients with early-stage CKD, sufficient protein intake to accomplish the repletion of protein depletion is appropriate with the restriction of protein intake only in the later stages of CKD. Supplementation with vitamins and minerals is generally recommended for patients with CKD unless a specific evidence of excess/increase or toxic levels is demonstrated.

Folic acid and vitamin B12: Beyond the standard recommendation for bariatric surgery patients, additional supplementation of folic acid and vitamin B12 is indicated in patients who have demonstrated deficiency of these nutrients.

Vitamin C: Vitamin C supplementation is recommended as in bariatric surgical patients without CKD and is routinely included in vitamin/mineral supplementation.

Vitamin D2/D3 and calcium: Insufficiency/deficiency of vitamin D is more prevalent in patients with CKD stages 3−5 than in the general population. It is, thus, reasonable to presume that additional supplementation of vitamin D2/D3 and calcium is necessary in bariatric surgical patients with CKD. Serum levels should be monitored to guide dosage to ensure adequate intake.

Vitamins E and A: Research is incomplete regarding the role of CKD in determination of the appropriate intake of vitamins E and A. Thus routine supplementation is recommended in the standard supplement doses following bariatric surgery.

Vitamin K: Vitamin K is a fat-soluble vitamin and, thus, may be malabsorbed in patients following malabsorption procedures. The primary manifestation is coagulopathy. Studies of vitamin K status include studies of coagulation. An increased requirement for CKD patients following bariatric surgery, however, has not been clearly demonstrated.

Trace minerals: There is a lack of definitive research regarding a requirement for higher doses of supplementation of selenium, zinc, or other trace minerals in bariatric surgery patients with CKD. Thus continuation of the recommended daily allowance is recommended.

Bariatric surgery post kidney transplant: There are no immediate specific recommendations regarding kidney transplant patients, other than careful attention to the development of nutritional deficiencies, including protein, minerals, and vitamins to guide supplementation. In general, postbariatric surgery and kidney transplantation patients should be managed as usual for bariatric surgical patients.

Role of bariatric surgery in chronic kidney disease

Several studies have addressed the impact of bariatric surgery on kidney disease. The first such published report matched 985 adults with a mean baseline estimated glomerular filtration rate (eGFR) of 97 mL/min/1.73 m^2 who underwent bariatric surgery (primarily gastric bypass) with 985 propensity-matched controls [51]. Over a median follow-up of 4.4 years bariatric surgery patients had a 58% lower risk of a decline in eGFR of $\geq 30\%$ [hazard ratio 0.42 (0.32, 0.55)] and a 57% lower risk of doubling in serum creatinine or ESKD [0.43 (0.26, 0.71)] compared to controls. In that study the definition of ESKD included patients with an eGFR < 15 mL/min/1.73 m^2 (*N*, surgery = 14, controls = 40) who were not necessarily on dialysis as well as persons requiring dialysis or transplantation (*N*, surgery = 8, controls = 10).

Kidney outcomes were also measured in a nonprespecified secondary analysis of the Swedish Obese Subjects study, which is an ongoing prospective observational trial in 2010 patients with mean baseline eGFR of 92 mL/min/1.73 m^2 who underwent bariatric surgery (vertical banded gastroplasty 68.1%, gastric band 18.7%, gastric bypass 13.2%) and 2037 matched controls [52]. Over 22 years the cumulative incidence of ESKD, defined as a composite endpoint of eGFR < 15 mL/min/1.73 m^2, dialysis, or kidney transplantation was reduced by 73% in the bariatric surgery cohort compared to controls after adjustment for confounding baseline factors [0.27 (0.12, 0.60)] (Fig. 41.3). However, the incidence of ESKD was very low overall (bariatric surgery = 13; controls = 26) and the number of subjects reaching each specific endpoint was not reported.

Friedman et al. studied the impact of bariatric surgery in 2144 adults enrolled in the National Institutes of Health-sponsored multicenter, prospective Longitudinal Assessment of Bariatric Surgery-2 (LABS-2) cohort, which was designed to study the long-term safety and efficacy of bariatric surgery [53]. The primary renal outcome was CKD prognostic risk, which was measured using established criteria that combined eGFR and albuminuria, the two main clinical indicators of CKD. By year 7 of follow-up, bariatric surgery was associated with improvement in CKD risk, even in patients with higher CKD risk at baseline (proportion of patients with improvement by baseline CKD risk: moderate—53%, high—56%, very high—23%). Importantly, the study did not include a comparison group, and the median baseline eGFR was 96 mL/min/1.37 m^2.

In the only published study performed exclusively in patients with CKD, Imam et al. compared propensity-matched patients who underwent gastric bypass or sleeve gastrectomy with patients who were referred for but did not have bariatric surgery. At baseline, 66% of individuals had diabetes and a mean eGFR of about 47 mL/min/1.73 m^2 [54]. At 3 months postsurgery the mean eGFR in the bariatric surgery cohort rose significantly (in mL/min/1.73 m^2 by surgery type: gastric bypass: +17; sleeve gastrectomy: +12) while remaining essentially unchanged in the control group. The statistically significant increase in eGFR in the bariatric surgery cohort persisted over the 3-year follow-up period, although the difference between groups narrowed over time.

Recent studies have also focused on the subgroup of patients with type 2 diabetes and CKD. This is an area of great importance because diabetic kidney disease is the most common cause of CKD and ESKD worldwide [55]. In light of the close relationship between obesity and the development of diabetes, it is possible that by improving the diabetic milieu bariatric surgery could halt or possibly even reverse diabetes-induced kidney damage.

O'Brien and colleagues retrospectively examined the likelihood of developing incident diabetic nephropathy, defined by at least two measurements of eGFR < 60 mL/min/1.73 m^2 separated by 90 days with no intervening higher levels, in 4024 bariatric surgery

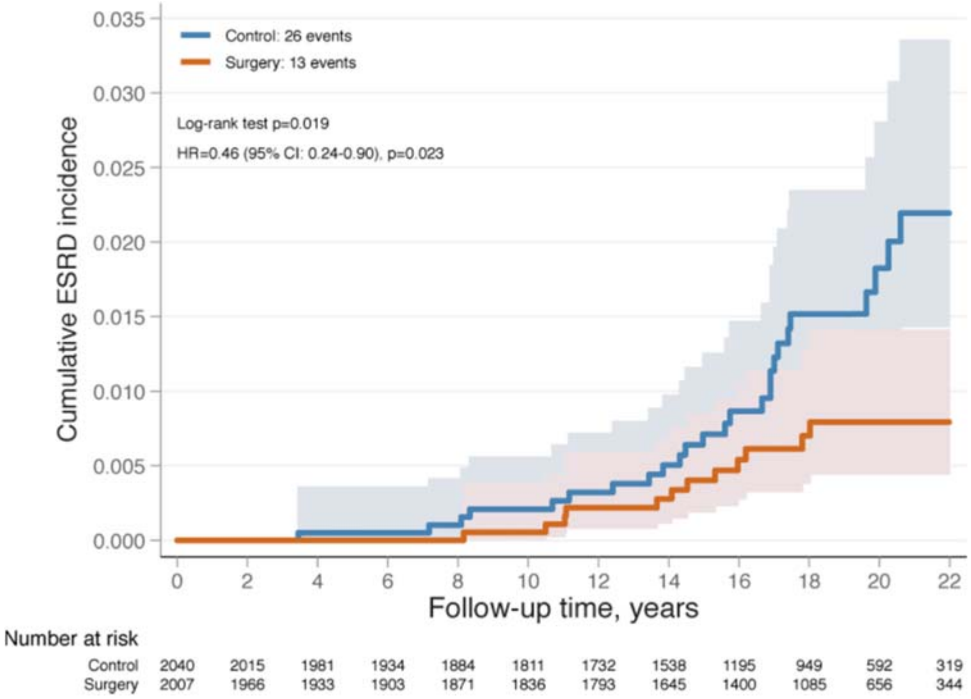

FIGURE 41.3 Kaplan−Meier estimates of cumulative incidence of ESKD in the control group compared to the surgery group. Shaded areas in the graph represent 95% CIs of the cumulative incidence. The *x* axes are truncated at 22 years but all observations after 22 years were included in the analyses. *CI*, Confidence interval; *HR*, hazard ratio. Source: *Reprinted with permission from Paddon-Jones D, Sheffield-Moore M, Katsanos CS, Zhang XJ, Wolfe RR. Differential stimulation of muscle protein synthesis in elderly humans following isocaloric ingestion of amino acids or whey protein. Exp Gerontol 2006;41(2):215−9.*

patients and 11,059 matched controls with severe obesity and type 2 diabetes [56]. As compared to controls, the hazard of incident diabetic nephropathy dropped in the bariatric surgery patients by as much as 81% [0.19 (0.14−0.27)] by year 2 after which it rebounded and then stabilized by year 7 [0.45 (0.29−0.71)]. While the study did not measure effects on albuminuria, a separate report described how bariatric surgery led to a 50% regression in microalbuminuria by 5 years in patients with type 2 diabetes [57].

In the Swedish Obese Subjects study, patients with type 2 diabetes showed only a trend toward a lower incidence of ESKD [0.41 (0.14−1.18)] after bariatric surgery, though this could have been due to a relatively low event rate [52]. However, patients with higher circulating insulin, worse glycemic control, and greater albuminuria—a profile that fits many individuals with diabetes/diabetic kidney disease—had among the very lowest incidence of ESKD.

The LABS-2 consortium performed a separate analysis in all 737 bariatric surgery patients with type 2 diabetes to determine if remission of type 2 diabetes up to 5 years after surgery improved markers of kidney disease and whether gut hormones and peptides modified these effects [58]. Bariatric surgery was associated with a lower risk of increased albuminuria and stabilization in the prognostic risk for CKD but it did not influence impaired eGFR. Interestingly, the gut peptide ghrelin modified the relationship between surgery and the prognostic risk for CKD in a protective manner. In addition, the presence of kidney disease prior to surgery reduced the likelihood of diabetes remission after surgery. This is the first study in bariatric surgery patients to examine the relationship between gut hormones/peptides and kidney-related outcomes and to evaluate how preexisting CKD affects diabetes remission rates.

In a propensity-matched analysis in obese persons with type 2 diabetes and normal baseline kidney function, 2287 bariatric surgery patients were compared to 39,267 controls over a median follow-up of 3.9 years [59]. Patients undergoing surgery were found to have a lower incidence of major adverse cardiovascular events, including nephropathy [0.40 (0.31−0.52)], which was defined as two measures of eGFR < 60 mL/min/1.73 m^2 at least 90 days apart with no intervening higher values.

Kidney benefits have also been observed in younger cohorts. One study frequency matched 30 obese adolescents with type 2 diabetes who underwent bariatric surgery with 63 youths who received medical therapy−based weight loss, all of whom had generally normal baseline kidney parameters [60]. Over 2 years of follow-up the number of patients with an eGFR < 90 mL/min/1.73 m^2 and a urinary albumin–creatinine ratio (UACR) > 30 mg/g dropped from 7 to 0 and 8 to 1, respectively, in the bariatric surgery group, while no significant changes were observed in the medical therapy group.

Data from randomized trials are limited [51]. The Surgical Treatment and Medications Potentially Eradicate Diabetes Efficiently trial was a single-center trial that randomized 150 obese patients with type 2 diabetes to intensive medical therapy alone, intensive medical therapy plus gastric bypass, or intensive medical therapy plus sleeve gastrectomy. While the primary outcome focused on glycemic control, kidney outcomes were included as a prespecified secondary endpoint. However, because persons with a serum creatinine ≥ 1.8 mg/dL were excluded from the outset, the population had normal baseline kidney function (median serum creatinine 0.7 mg/dL, median eGFR 106–110 mL/min/1.73 m^2, median UACR 6–12 mg/g). At 5 years postsurgery the UACR had fallen significantly in the sleeve gastrectomy group only [absolute decrease −5.0 mg/g (−15.0, −1.0)] as compared to the medical therapy group (<0.001). Also observed in the two surgery groups only, were within-group reductions in serum creatinine and eGFR.

Role of bariatric surgery in kidney transplant

Bariatric surgery is considered for patients with obesity who are either candidates for kidney transplant, or struggling with weight loss post-kidney transplant. In the case of candidates for kidney transplant, many programs preclude patients with a BMI of >35 or 40 kg/m^2 from being wait-listed based on increased perioperative complications. The evidence shows an increased risk of delayed graft function [61,62], wound infection [62], and length of hospitalization [62] in patients with obesity undergoing transplant. The risks of graft survival and mortality are less clear, with some studies showing decreased graft survival and increased mortality with increasing BMI > 30 kg/m^2, while other studies fail to show this [61]. Outcomes may differ secondary to inconsistent study populations, methods, or adjustment for comorbidities. There is clear evidence, despite BMI-related complications, that survival outcomes for all BMI categories post-kidney transplant are superior versus being on dialysis [63].

Bariatric surgery as a bridge to meet lower BMI requirements pretransplant has increased nine-fold from 2006 to 2016 [64]. Gastric bypass, yielding greater weight loss versus gastric band, was the historically preferred pre-kidney transplant. Now, >85% of ESKD patients undergo sleeve gastrectomy [64]. Sleeve gastrectomy (vs gastric bypass) may stabilize reported inconsistent absorption of immunosuppressive medications [65] required for graft survival. Nutritional challenges of iron, vitamin D, and calcium in ESKD potentially exacerbated after gastric bypass, are less problematic after sleeve gastrectomy. While sleeve gastrectomy does produce significant, rapid weight loss, there is greater variation of weight loss [26,29], and long-term studies versus gastric bypass comparing posttransplant weight-loss durability or mortality have not been done.

Post-kidney transplant patients may develop obesity severe enough to meet the indications for bariatric surgery. Compared with matched controls, patients who undergo bariatric surgery post transplant experience sustained weight loss and improved graft and patient survival [66]. Concern for infection in the context of immunosuppression, or placing a patient at nutritional risk, should their transplanted kidney fail, are important considerations. Similar to a peritoneal dialysis catheter, the gastric band is a foreign body and may require removal in the event of blood–borne or abdominal infection. Should a graft fail with return of ESKD, a bypassed duodenum after gastric bypass or BPD/DS will present iron and calcium absorption challenges. Sleeve gastrectomy, posing neither potential infectious disease nor nutritional risks, may be the safest option.

Cost/benefit bariatric surgery

The true costs of bariatric surgery over time, both in dollars and long- and short-term harm, are not easily determined. There is an initial increased cost to undergo the operation ($15,000–25,000), and additional required follow-up encounters for postoperative nutritional and surgical care. Uncommonly, patients may need hospitalization for surgical complication management—technical complications such as leak (<1%) [34,35], as well as routine postoperative nausea, vomiting and/or dehydration (<10%–20%) [36]. Improved safety of bariatric operations [36] and enhanced surgical recovery programs [67] contribute to decreasing need for hospitalization in the month after surgery.

There may be an overall savings in health-care dollars downstream with improved health. The literature shows evidence for cost savings in the first few years for prescription drugs and number of health-care encounters [68–70]. As health improves with weight loss after bariatric surgery, increased cost can ensue from treatments previously withheld. Elective operations, such as joint replacement or solid-organ transplant, increase secondarily as required minimum BMI thresholds are met.

Plastic surgery demand for the reduction of excess skin also increases after significant weight loss and represents an increase in out-of-pocket expense.

Long-term studies on cost effects of increased longevity because of decreased comorbidities are lacking. The cost/benefit ratio is different for different patient subgroups. The subgroup with type 2 diabetes is financially costly to a health-care system and remission and/or partial remission of diabetes occurs in 28%−90% of patients with weight loss after bariatric surgery. Remission/partial remission of diabetes brings a significant cost savings in prescription medications and the avoidance of costly long-term complications, including dialysis for kidney failure, blindness, limb amputation, cardiovascular disease, and cerebrovascular events. Interrupting the progression of kidney disease with weight loss after bariatric surgery, and eliminating the need for dialysis, bears researching to determine its quality of life and cost value.

Overall the cost-effective modeling and analyses for bariatric surgery are based primarily on gastric bypass and band outcomes. Current literature is relatively limited in our era of sleeve gastrectomy dominance. Analyses of long-term data generated by closed systems, such as health-maintenance organizations, or nationalized health-care systems, which include sleeve gastrectomy as well as gastric bypass, may provide the best answers to overall and patient-subgroup cost or savings after bariatric surgery.

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CHAPTER

42

Nutritional and metabolic management of the diabetic patient with chronic kidney disease and chronic renal failure

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Introduction

Diabetes mellitus (DM) has for sometime been the single largest contributor to the growing prevalence of chronic kidney disease (CKD) worldwide, rising over three decades in concert with the rising prevalence of diabetes itself. In the United States, 23% of all adults 60 years and older have DM [1]. It is estimated that the worldwide prevalence of DM will reach about 450 million people by the year 2030 [2]. Diabetic nephropathy affects 10%–20% or more of individuals with DM, the majority of whom have type 2 diabetes. While the risk of incident end-stage renal disease (ESRD) attributed to diabetes appears to have stabilized in the United States and elsewhere, the incidence of DM as well as its overall prevalence continue to increase. In a recent cross-sectional study of National Health and Nutrition Examination Survey (NHANES) data, about a quarter of CKD among all US adults was attributable to diabetes, after adjusting for demographic variables such as age and hypertension [3]. Diabetes is now the presumed cause of approximately half of incident ESRD cases [4], and its prevalence is expected to rise with the rising prevalence of ESRD in coming decades, although there may be an element of overreporting of the condition, which may not necessarily be the primary cause of the ESRD in a given patient [4]. Nonetheless, the dramatic rise in the global burden of disease and death attributed to diabetic kidney disease is among the highest for all chronic diseases [5]. The top three countries in terms of prevalence of diabetes are the United States, China, and India, with distributions of diabetic kidney disease shown in Fig. 42.1 [6].

The prevalence of the hallmark components of CKD [albuminuria and reduced glomerular filtration rate (GFR)] rises progressively with longer diabetes duration. Albuminuria and estimated GFR (eGFR) are predictors of ESRD and mortality in diabetic CKD. Because the combination of eGFR and albuminuria predicts outcomes better than either measure alone [7], risk assessment based on CKD staging level is increasingly utilized, including albuminuria to add prognostic information. It is clear that early and later phases of diabetic CKD may respond differently to similar therapeutic strategies. Multiple detection, prevention, and interventional studies have resulted in several treatment strategies of proven benefit. Standard guideline-based therapy for diabetic CKD consists of tight glycemic control, intensive management of hypertension, and aggressive use of renin-angiotensin system (RAS) blockade. Randomized trials have consistently demonstrated the benefit of RAS blockade [particularly with angiotensin-converting enzyme inhibitor (ACEI) and angiotensin receptor blockades (ARBs)] in slowing progression of CKD in both type 1 and type 2 DM.

Nonetheless, the limitations of RAS blockade in diabetic CKD are evident, as the decline in kidney function despite treatment remains higher than that expected due to aging [8]. Meanwhile, concerns remain about the limitations of tight glycemic control, the use of blockade with combinations of RAS medicines, and disappointing development of newer therapies, although increasing evidence suggests that sodium D: glucose D-transporter 2 (SGLT2) inhibitors will help fill that void [9,10]. With or without standard therapy, significant numbers of patients with DM will continue to progress

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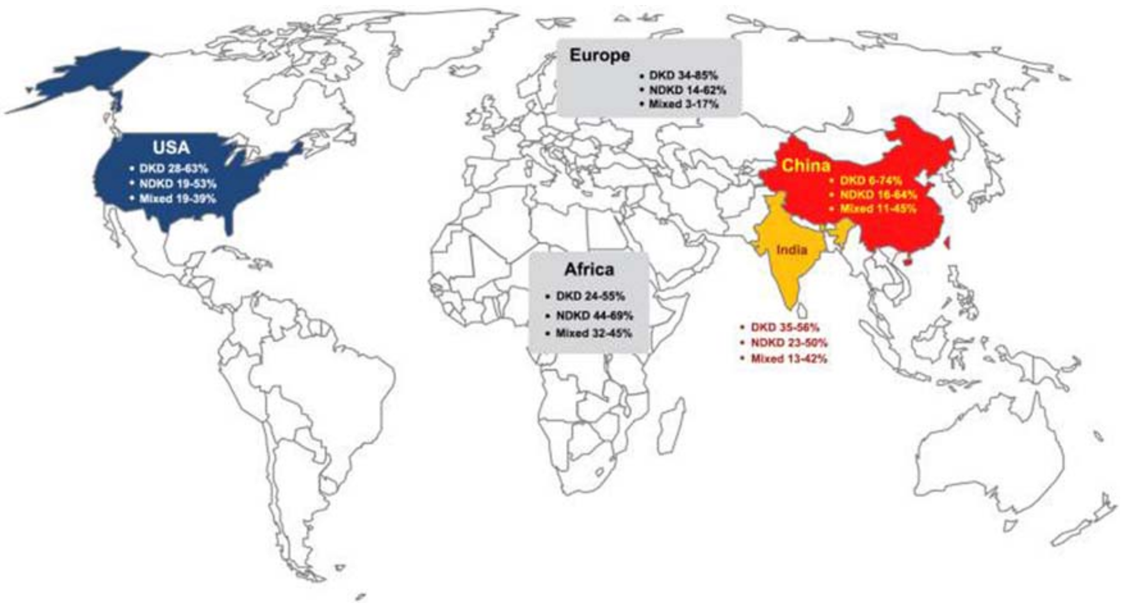

FIGURE 42.1 Diagnostic distributions of diabetic kidney disease, nondiabetic kidney disease, or mixed forms based on diabetes patients biopsied from different institutions worldwide [6].

through the stages of CKD. As diabetic CKD worsens, it becomes more of a systemic disease. When combined, DM and CKD pose a double threat in terms of nutritional and metabolic abnormalities. This chapter presents the pathogenesis and clinical consequences of disorders of nutrition and metabolism in the diabetic CKD patient.

Glucose/insulin homeostasis

Glycemic management in patients with CKD is complicated by alterations in insulin and glucose homeostasis. Insulin resistance (IR) and glucose intolerance are well-recognized features in patients with CKD. IR may be estimated from fasting glucose and insulin concentrations or determined more accurately by the gold-standard hyperinsulinemic–euglycemic clamp method [11]. Glucose transport is one of the major activities of insulin and is believed to be rate-limiting for glucose uptake in peripheral tissues (Fig. 42.2). The transport of glucose into cells is mediated by specific glucose transporter proteins. Insulin actions at the cellular level are complex but are known to include activation of intrinsic tyrosine kinase activities found in the receptor intracellular beta-subunit portion, intracellular responses, including generation of messengers for insulin, interiorization of the receptor–insulin complex within the cell, translocation of hexose transporter units into the plasma membrane from intracellular storage sites, and the downstream metabolic effects of the hormone [12].

Even nondiabetic CKD patients may have mild fasting hyperglycemia and decreased glucose tolerance [13]. In a recent study of 59 patients with moderate-to-severe nondiabetic CKD, two-thirds had impaired glucose tolerance due to a combination of reduced insulin sensitivity (by hyperinsulinemic–euglycemic clamp) and augmentation of insulin secretion that was inadequate to maintain normal glucose tolerance [14]. Regarding the latter, it has been suggested that urea itself impairs insulin secretion in CKD [15]. Disposal of glucose is inversely related to serum creatinine level [16]. IR may promote kidney disease by impairing renal hemodynamics through mechanisms such as increasing glomerular filtration, activating the sympathetic nervous system, retaining sodium, and decreasing Na,K-ATPase activity [17]. In fact, in a cross-sectional analysis of participants in the Third National Health and Nutrition Examination Survey, Chen et al. reported that IR estimated by the homeostasis model assessment (HOMA) was associated with an increased risk of having CKD [18]. Contributing factors to the abnormalities in glucose homeostasis in people with kidney impairment are shown in Fig. 42.3. Abnormal insulin metabolism involves reduction in renal insulin clearance that is typically present in advanced CKD, stages 4 and 5 [19]. Some evidence suggests that a reduction in pancreatic insulin secretion also occurs, is related to hyperparathyroidism and vitamin D deficiency, and improves with correction of these disorders [20,21]. In a recent clinical report of 120 CKD stages 2 and 3 patients (of whom 19 were being treated for diabetes), 42% suffered from vitamin D

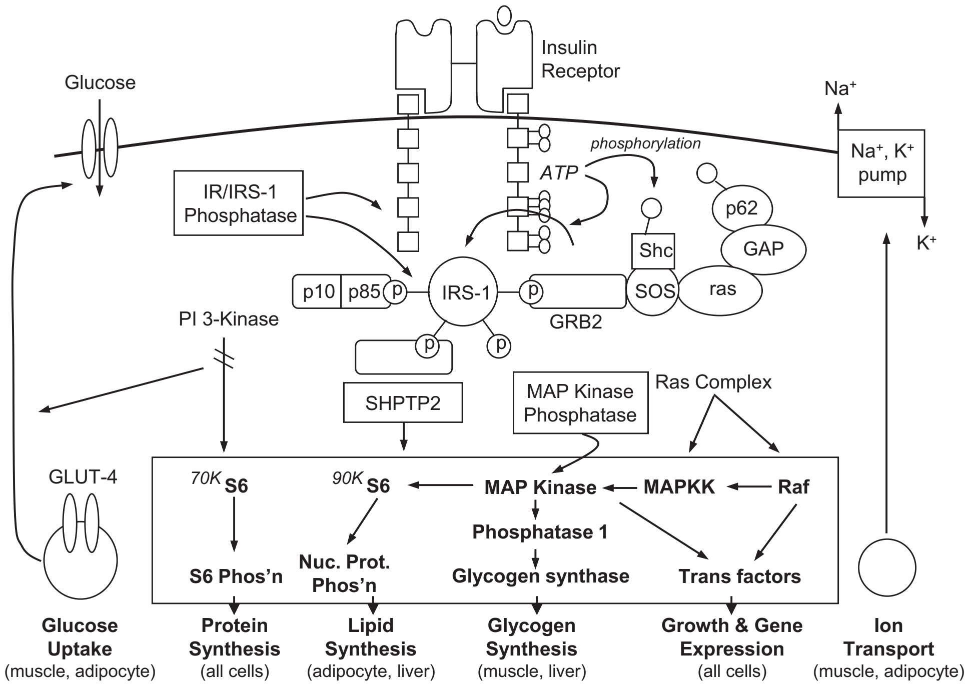
Insulin Receptor
Glucose
Na$^+$
Na$^+$, K$^+$ pump
K$^+$
phosphorylation
ATP
IR/IRS-1 Phosphatase
p62
GAP
Shc
SOS
ras
p10
p85
p
IRS-1
p
GRB2
PI 3-Kinase
p
p
SHPTP2
MAP Kinase Phosphatase
Ras Complex
GLUT-4
70K S6
90K S6
MAP Kinase
MAPKK
Raf
Phosphatase 1
S6 Phos'n
Nuc. Prot. Phos'n
Glycogen synthase
Trans factors
Glucose Uptake (muscle, adipocyte)
Protein Synthesis (all cells)
Lipid Synthesis (adipocyte, liver)
Glycogen Synthesis (muscle, liver)
Growth & Gene Expression (all cells)
Ion Transport (muscle, adipocyte)

FIGURE 42.2 Schematic representation of the tetrameric insulin receptor and activation of insulin-triggered cellular events in responsive tissues. In activating cellular glucose transport and disposal pathways, insulin first binds to the alpha-subunit of its receptor. Complex effects executed through the insulin signaling pathways and leading to the metabolic actions of insulin are shown.

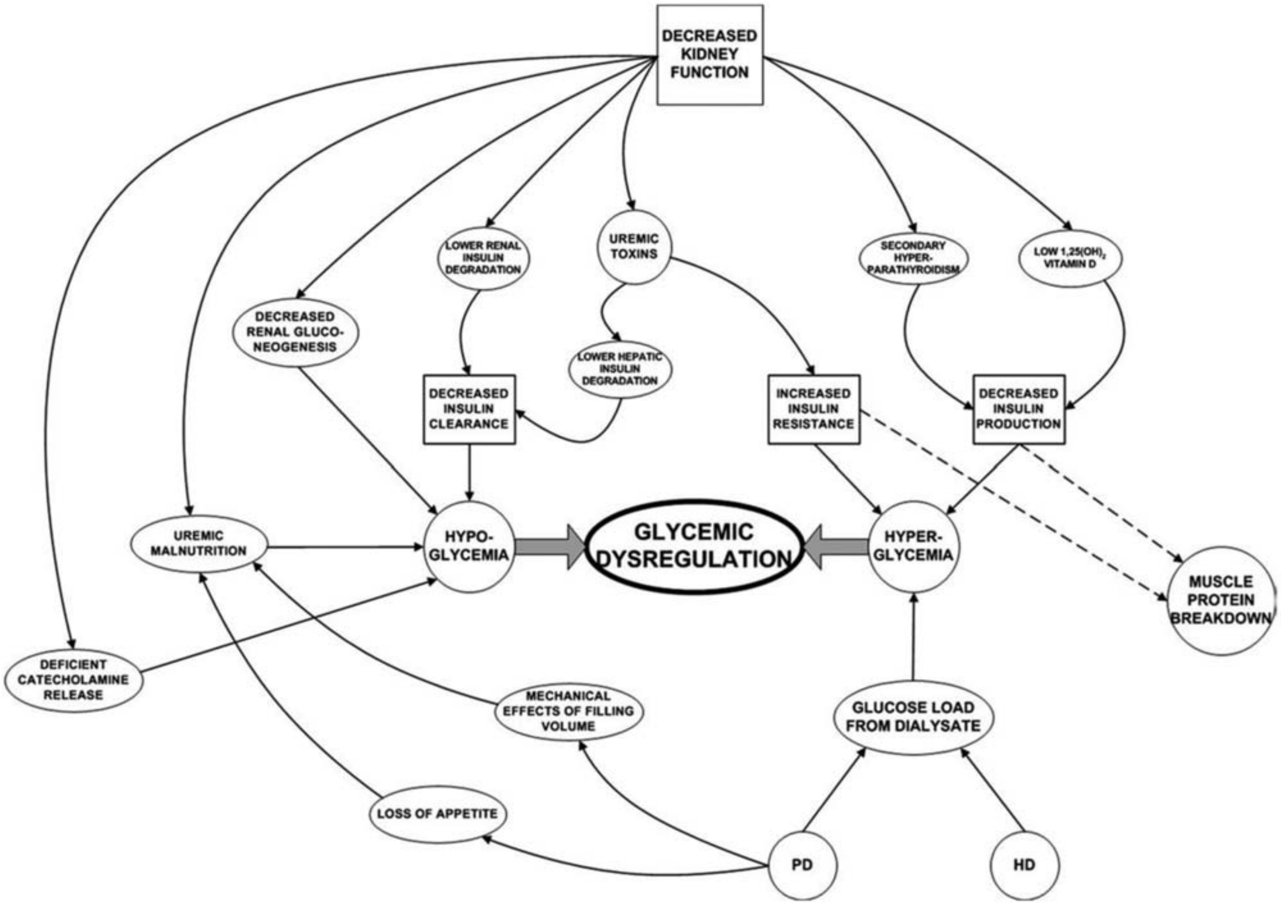
DECREASED KIDNEY FUNCTION
LOWER RENAL INSULIN DEGRADATION
UREMIC TOXINS
SECONDARY HYPER-PARATHYROIDISM
LOW 1,25(OH)$_2$ VITAMIN D
DECREASED RENAL GLUCO-NEOGENESIS
LOWER HEPATIC INSULIN DEGRADATION
DECREASED INSULIN CLEARANCE
INCREASED INSULIN RESISTANCE
DECREASED INSULIN PRODUCTION
UREMIC MALNUTRITION
HYPO-GLYCEMIA
GLYCEMIC DYSREGULATION
HYPER-GLYCEMIA
MUSCLE PROTEIN BREAKDOWN
DEFICIENT CATECHOLAMINE RELEASE
MECHANICAL EFFECTS OF FILLING VOLUME
GLUCOSE LOAD FROM DIALYSATE
LOSS OF APPETITE
PD
HD

FIGURE 42.3 Overview of glucose/insulin homeostasis in chronic kidney disease/ESRD. Disturbances of glucose metabolism include insulin resistance and glucose intolerance. Several factors contribute to hypoglycemia, which may coexist with hyperglycemia. *ESRD*, End-stage renal disease; *PD*, peritoneal dialysis; *HD*, hemodialysis. *Adapted from Kovesdy C, Sharm K, Kalantar-Zadeh K, et al. Glycemic control in diabetic CKD patients: where do we stand? Am J Kidney Dis 2008;52:766–77.*

insufficiency and 41% were moderately deficient [22]. Research on the metabolic profiles of pancreatic islets during progression of chronic renal failure has suggested that glucose-induced insulin secretion is impaired because of alterations in closure of ATP-dependent potassium channels and reduction in glucose-induced calcium signaling [23]. Other recent research has explored the mechanisms and clinical significance of IR in CKD. It is commonly understood that IR is a characteristic feature of uremia, regardless of the cause of renal disease. In insulin-resistant states, insulin-stimulated cellular glucose uptake is impaired; other insulin actions such as suppression of glycogenolysis, gluconeogenesis, lipolysis and fatty acid release, protein catabolism, and cellular potassium and phosphate uptake may not be similarly impaired [24].

A recent cross-sectional study of 128 diabetic patients from India assessed the degree of IR in those with different stages of diabetic kidney disease (microalbuminuria, macroalbuminuria) as compared to those with normoalbuminuria [25]. IR was calculated using the HOMA method. There was no significant difference between the study groups with regard to age, body mass index, duration of diabetes, or glycemic control. Mean HOMA-IR increased significantly with worsening renal disease ($P < .0001$). In contrast, when 73 nondiabetic CKD patients were evaluated for IR, HOMA-IR did not differ in patients with or without a renal ESRD endpoint, and even after over 24 months of follow-up, the GFR level was not associated with the degree of IR [26]. In reality, IR is somewhat variable in kidney disease, as it is in such other conditions as type 2 diabetes, obesity, or even in normal subjects [27]. Numerous studies suggest that IR in uremia appears to be restricted to defects in glucose uptake and muscle protein anabolism. The ability of insulin to stimulate peripheral glucose disposal by muscle and adipose tissue is markedly impaired, while hepatic glucose uptake is normal and hepatic glucose production is suppressible in uremia [28]. At least two other insulin-mediated effects, its antiproteolytic action and translocation of potassium into cells, are not impaired in advanced renal failure [28,29].

Mechanisms of IR are complex. In general, IR may take the form of defective uptake, metabolism, or storage of glucose in its target tissues (muscle, liver, and adipose tissue) related to alterations in insulin signaling at receptor or postreceptor locations [30], It is now understood that IR results not from defects in binding of insulin to its receptor on the cell membrane, but to interference with intracellular signaling beyond the receptor [31]. Selective impairment of insulin signaling cascades due to IR may also occur in the kidney [32]. IR in uremia is an acquired defect in the insulin receptor signaling pathway. Stimulation of glucose transport is one of the major activities of insulin and is believed to be rate-limiting for glucose uptake in peripheral tissues [33]. Central to the biologic actions of insulin, insulin signaling occurs when insulin binds to its receptor, a tyrosine kinase, which then phosphorylates insulin receptor substrates such as IRS1 [34]. Recruitment of multiple downstream targets such as glycogen synthase protein kinase C, endothelial nitric oxide synthase, and others elicit wide-ranging effects, including enhancement of glucose uptake, glycogenesis, lipogenesis, and cellular proliferation [35]. In muscle and adipose tissue, insulin stimulates glucose uptake by promoting translocation of an intracellular pool of glucose transporters to the plasma membrane. Physiological studies have shown that kidney tissues are also responsive to insulin. Moreover, IR in the glomerulus is similar to the IR found in the endothelium of other vascular tissues. This resistance could contribute to the initiation and progression of glomerular lesions in diabetes, in combination with the abnormal pathophysiology in the mesangial cells and podocytes [36]. IR also appears to involve sites distal to the insulin receptor, from the generation of intracellular messengers for insulin [37] to glucose transport to effects of insulin on one of the intracellular enzymes involved in glucose metabolism itself [38].

The mechanisms behind IR in CKD patients are incompletely understood. The improvement in insulin sensitivity associated with dialysis suggests a role for uremic toxins [39,40]. Recent data suggest that alterations in metabolism with CKD may alter adipose tissue secretion patterns independently of obesity. Released adipokines then become an important source of proinflammatory molecules that cause IR [41]. Plasma adiponectin levels are inversely associated with kidney function, and increased adiponectin concentrations may contribute to IR [42]. The production of proinflammatory molecules in adipose tissue may also be modulated by oxidative stress [43]. Yet another factor, erythropoietin deficiency, might contribute to IR. This possibility was suggested by a recent study that showed recombinant erythropoietin-treated hemodialysis patients had lower mean insulin levels and (HOMA-IR) levels than those not treated with erythropoietin [44].

The clinical relevance of insulin and IR in the CKD patient is not fully understood [45]. Renal tissues are responsive to insulin, especially in its renal tubular effects to regulate glomerular endothelial cells [36] and podocytes [46], enhance proximal tubular sodium reabsorption [47], and interact with the renin—angiotensin system [48]. IR promotes kidney disease by impairing renal hemodynamics through mechanisms such as activation of the sympathetic nervous system, sodium retention, increased glomerular filtration, and decreased Na,K-ATPase activity [49]. IR may contribute to protein-energy wasting, atherosclerosis, and cardiovascular complications in CKD/ESRD patients. One important consequence of IR is protein-energy wasting [50]. Dialysis patients even without DM or obesity have measurable IR associated with increased muscle protein breakdown. Uremic IR contributes to muscle wasting, weakness, and frailty through a form of "bioenergetics failure" involving mitochondrial dysfunction and muscle proteolysis [51]. Muscle protein breakdown in renal failure is at least partly mediated through the ubiquitin–proteasome pathway and is related to suppression of phosphatidylinositol-3 kinase [52,53]. A recent report examined the relationship between HOMA and fasting whole-body and skeletal muscle protein turnover to determine mean skeletal muscle protein synthesis, breakdown, and net balance in nondiabetic chronic hemodialysis patients [54]. An inverse relationship between net skeletal muscle protein balance and HOMA was noted.

Progress in understanding the development of IR in the kidney was recently reported by Mima et al. [36]. These investigators conducted the first comparative analysis of insulin signaling and cellular actions involving the renal glomerulus and tubules; these processes were evaluated in diabetic, insulin-resistant, and control states. It is known that in diabetes, the actions of insulin on the glomerulus may be blunted [35]. After insulin binds to its receptor, downstream targets recruited include Akt, glycogen synthase kinase 3, Ras, extracellular signal-regulated kinase (ERK), and protein kinase C. Activation of these targets elicit wide-ranging metabolic effects. Mima et al. [36] characterized dysfunctional insulin signaling in glomeruli and tubules of diabetic and insulin-resistant animals and suggested that some of these alterations may contribute to diabetic glomerulopathy.

Increased attention has been given recently to the contribution of the kidneys to glucose homeostasis through processes that include renal insulin clearance, as well as gluconeogenesis and glucose filtration and resorption [55]. Roughly a quarter of insulin produced daily by the normal pancreas is cleared by the kidneys, through filtration and tubular secretion, although luminal insulin is so thoroughly taken up by endocytosis that little of the filtered insulin ends up in the urine [33]. However, a much larger portion of administered insulin is renally cleared, as it enters the circulation while bypassing the liver. Normally, up to 180 g of glucose may be filtered each day by the glomerulus, and nearly all of this glucose is reabsorbed in the proximal tubule. This resorption is mediated as secondary active transport through two SGLT proteins. The majority of glucose resorption occurs through sodium D: glucose D-transporter 2 (SGLT2), present in the S1 segment of the proximal tubule [56]. Increased reabsorption of glucose by the kidneys occurs in type 2 diabetes and is a target of recently developed hypoglycemic agents. Various glucoside compounds have been synthesized that have a high affinity for SGLT2 [57]. Because of their ability to prevent glucose reabsorption and increase urinary glucose excretion, SGLT2 inhibitors have now been approved as an insulin-independent treatment for diabetes [58]. Available information indicates that the administration of SGLT2 inhibitors can induce glucosuria and improve glycemic control in patients with type 2 diabetes without the risk of inducing severe hypoglycemia [59].

Value of glycemic control and its determination in CKD

The hemoglobin A1c (HbA1c) target and the value of glycemic control in CKD/ESRD continue to be debated. For reasons reviewed next, the benefits of tight glycemic control may be difficult to determine [60]. The previously recommended HbA1c targets in the setting of CKD are in many cases identical to those for the general diabetic population, that is, <7% regardless of the absence or presence of CKD. More recent guideline recommendations have broadened HbA1c targets in the CKD population [61]. Recent observational studies have been consistent in calling into question this approach and established the limitations of HbA1c in advanced CKD while providing somewhat contrasting results and significant methodological differences [62–64]. The single biomarker HbA1c, used in these observational studies, remains the most widely used indicator tool and gold standard of integrated long-term glycemic control in the diabetic population [65]. HbA1c is used clinically to make therapy adjustments and as a marker of risk of complications. For two decades, since the seminal diabetes control and complications trial (DCCT) [66] and United Kingdom prospective diabetes study (UKPDS) [67] demonstrated that HbA1c levels strongly predict the risk of microvascular complications associated with type 1 and type 2 DM, respectively, the glycohemoglobin level has been the primary basis of diabetes management. Indeed, the strength of the association between glycemic control and clinical outcomes is reliant on the relationship between hyperglycemic and elevated HbA1c levels. It has recently been proposed that HbA1c can be used to report estimated average serum glucose levels [68]. HbA1c is a minor component of hemoglobin, comprising about 4% of total hemoglobin in normal adult erythrocytes. The HbA1c level as a marker of hyperglycemia reflects average blood glucose concentration over roughly the three preceding months [69]. Good correlation between HbA1c and blood glucose levels in patients with preserved kidney function has been reported in the

Diabetes Control and Complications Trial [66] and the A1c-Derived Average Glucose study [70]. The American Diabetes Association recommends using point-of-care A1c testing to guide management with a goal of lowering A1c to below 7% [2]. A recent epidemiologic study and an opinion article suggested that HbA1c may be a risk factor for ESRD and mortality in the nondiabetic CKD population [71,72].

However, its unreliability has been recognized in a number of clinical conditions [73], particularly hematologic diseases involving anemia or hemolysis, and has been attributed to the analytical, biological, and clinical variability associated with HbA1c. Analytical variability has resolved with introduction of newer assay methods [74]. Nonetheless, biological and clinical variability of HbA1c continue to limit its application to individual patients, even in the general diabetic population. One source of the variability is differential glycation rates, which appear to vary significantly among individuals. The relationship between HbA1c and time-averaged serum glucose levels also varies across racial backgrounds [73].

More recently, discordances from other measures of glycemic control in clinical studies [75] have raised concerns about the validity of A1c in predicting outcomes in the setting of advanced CKD/ESRD. The Kidney Disease Outcomes Quality Initiative (KDOQI) guidelines for diabetic kidney disease acknowledge that data for validating methods for monitoring glycemia in kidney impairment are severely lacking. For example, a recent United States Renal Data System report indicated that the prevalence of patients with A1c levels over the 7% target was 63% for stages 1 and 2 CKD but fell to 46% in stages 3 and 4 CKD [76], in whom factors such as anemia, typically due to a reduced erythrocyte life span, administration of erythropoietin, blood transfusions, and metabolic acidosis, could affect the reliability of the A1c results [77]. In our large national ESRD database analysis, the mean HbA1c value was only 6.77%, and values over 7.0% were found in only 35% of patients [62]. Unlike the high-performance liquid chromatography assay previously used in routine laboratory A1c testing, the contemporary immunoturbidimetric assay methodology is not influenced by high serum urea nitrogen levels. Nonetheless, A1c may not optimally represent the glycemic state in advanced kidney disease due to the unique changes in physiology. The most cited influences on A1c variability in kidney patients are anemia and the use of erythrocyte-stimulating agents (ESAs). HbA1c indicates the percentage of circulating hemoglobin that has chemically reacted with glucose. Reduced erythrocyte survival in ESRD would be expected to lower HbA1c levels by reducing the time for exposure to ambient glucose [78]. In addition, the widespread use of ESAs increases the proportion of immature red blood cells in the circulation, with less propensity for glycosylation. One report described a false lowering of A1c with both erythropoietin and darbepoetin analogs in a single patient [79]. As a result, HbA1c levels tend to be lower in diabetic patients with kidney impairment or who are undergoing renal replacement therapy [80]. Peacock et al. measured levels of glycated hemoglobin (HbA1c) and glycated albumin (GA) in 307 patients with diabetes, of whom 258 were undergoing maintenance hemodialysis and the remaining number of patients were without overt kidney disease [80]. In patients undergoing maintenance hemodialysis, the ratios of GA to HbA1c were higher, suggesting that the HbA1c significantly underestimated serum glucose levels. A study by Chen et al. in patients with CKD stages 3 and 4 reported that the mean measured serum glucose levels were about 5%−10% higher than an estimated average glucose (AG) calculated from the same HbA1c, in comparison to the serum glucose in patients with normal kidney function [81]. These findings indicate that the HbA1c underestimates mean blood glucose levels in CKD. A recent small study contrasted 4-day continuous serum glucose monitoring (CGMS) in type 2 diabetic patients undergoing maintenance hemodialysis ($N = 19$) with a larger group of type 2 diabetic patients without nephropathy ($N = 39$) [82]. In all patients the CGMS results and glucose concentrations according to the glucose meter were similar. Glycated hemoglobin and mean glucose concentrations were strongly correlated in the nondialysis group ($r = 0.71$) but were weakly correlated in those undergoing hemodialysis ($r = 0.47$). Hemodialysis patients were receiving erythropoiesis-stimulating agents and had lower hemoglobin levels than the comparator group (11.6 vs 13.6 g/dL, $P < .0001$). These data also indicate that CGMS is a potential tool for understanding changes in glucose homeostasis related to the dialysis procedure itself [83]. A recent review confirmed the inferior correlation of HbA1c with glucose levels in the presence of CKD and emphasized the importance of self-monitoring of blood glucose [84]. Ongoing identifications of sources of variability in HbA1c levels have raised particular concern with regard to relying on this test as the sole measure of glycemia in the diabetic kidney disease population. Fructosamine, a generic test that refers to all glycated serum proteins, is increasingly available for the monitoring of diabetes treatment, particularly for short-term control, but does not correlate strongly with fasting serum glucose levels [73]. Fructosamine is effected not only by protein glycation, but also by the concentrations of individual plasma proteins, which are known to vary in CKD. The need to correct values for total protein or albumin concentrations remains unresolved [85]. Similar to the HbA1c findings, the study by Chen et al. reported that fructosamine levels were also lower than expected for the same glucose concentration in CKD patients, as compared to patients with normal kidney function [81].

While not as well-studied as HbA1c, evidence has accumulated that measurement of glycated albumin is valuable in assessing glycemic control [86,87]. The clinical usefulness of glycated albumin in CKD was recently reviewed [87]. Relative to HbA1c, GA may more accurately reflect glycemic control in diabetic patients with CKD/ESRD, where HbA1c is particularly unreliable. Albumin undergoes glycation similarly to hemoglobin and accounts for most of the serum glycated proteins. Because the turnover of serum albumin is shorter, (a half-life of approximately 20 days), it reflects a shorter glucose exposure and a potentially more sensitive metric of glycemia. Although not influenced by dialysis or the age or life span of erythrocytes, anemia, or erythropoietin, its precision may be limited in states of abnormal protein turnover, such as from inflammation, hypercatabolic states, peritonea dialysis, proteinuria, albumin infusions, or gastrointestinal protein losses. GA reflects glycemic control for only 1−2 weeks prior to obtaining the sample [88]. In patients with nephrotic proteinuria, GA levels may be falsely reduced. Confounders in GA testing include obesity, smoking, and hyperuricemia, all of which are prevalent in the diabetic CKD population [73]. The case for GA has been bolstered by an improved assay that is unaffected by changes in serum albumin. It has also been suggested that GA in vivo has biologic properties that could actually contribute to the pathogenesis of diabetic vascular or other complications [89], as an Amadori-modified reaction product capable of inducing oxidative stress, and enhance proinflammatory endothelial responses in the vessel wall. GA can be measured using a bromocresol purple method and calculated as the percentage relative to total albumin. A reference range of about 12% has been determined for nondiabetic American individuals with normal kidney function [80], with a somewhat wider reference interval compared to the more compressed range of measured values for HbA1c.

GA was deemed superior to A1c in assessing glycemic control in two studies of kidney patients [88,89]. In a large Japanese study of 538 maintenance hemodialysis patients with type 2 diabetes, 828 hemodialysis patients without diabetes, and 365 diabetic patients without significant kidney impairment, Inaba et al. [89] demonstrated significantly lower HbA1c levels relative to blood glucose or to GA levels in patients undergoing chronic dialysis, as compared to those without kidney impairment. The ratio of GA to HbA1c (with a previously reported ratio of approximately 3.0) was 2.93 in patients without CKD and 3.81 in those undergoing chronic dialysis. HbA1c levels were also higher in patients not treated with ESAs. GA levels were affected by glucose but not serum albumin levels. In a subsequent US study the GA/HbA1c ratio was also significantly higher in ESRD patients (2.72 vs 2.07) [80]. A recent analysis of 24 cross-sectional studies totaling 3928 patients investigated the correlation between GA and HbA1c and AG levels in patients with CKD [90]. The metaanalysis concluded that in the early CKD stages, there was no statistically significant difference between GA and HbA1c, while in advanced CKD, GA was superior to HbA1c in assessing glycemic control. Analysis indicated that in advanced CKD, HbA1c underestimated the glycemic conditions of patients.

Studies to clarify the utility of glycemic control and clinical outcomes in various stages of CKD and in ESRD have emerged. A recent review of randomized clinical trials concluded that patients who received treatment to achieve tighter glycemic control experienced lower risks of new onset microalbuminuria and progression of microalbuminuria [60]. Overall, the effects of tight glycemic control to reduce progression to advanced renal endpoints such as ESRD have been less conclusive. In a population-based cohort study from Canada, Shurraw et al. identified 23,296 people with diabetes and CKD who had baseline HbA1c results [91]. Over a median follow-up of 46 months, 401 developed ESRD. The excess risk associated with higher HbA1c levels varied from 22% (Hgb 7%−9%) to 152% (Hgb higher than 9%) in those with stage 3 CKD, but the corresponding increases were only 3% and 13% in those with Stage 4 CKD. A recent report of 2401 patients demonstrated that higher baseline HbA1c levels were associated with higher risk of renal replacement therapy and all-cause mortality in patients with stages 3 and 4 CKD [92], but not for stage 5 CKD. Secondary analysis of the ADVANCE (Action in Diabetes and Vascular Disease: Preterax and Diamicron-Mr Controlled Evaluation) trial reported a reduced risk for ESRD with intense glucose control [93], while other studies showed no benefit [94]. A recent cohort study of 6165 patients with diabetes and CKD stages 1−5 using HbA1c as categorical and continuous predictor concluded that HbA1c levels were not associated with ESRD risk, although both low and high HbA1c levels increased risk of all-cause mortality [95]. Nonetheless, in a study that focused on 17,819 US Veterans with late-stage diabetic CKD who transitioned onto dialysis, higher mean HbA1c levels (≥8%) during the 1-year prelude before ESRD were associated with worse 1-year post-ESRD mortality [96].

A series of studies have addressed the issue of optimal glycemic targets in ESRD [97,98] and suggested

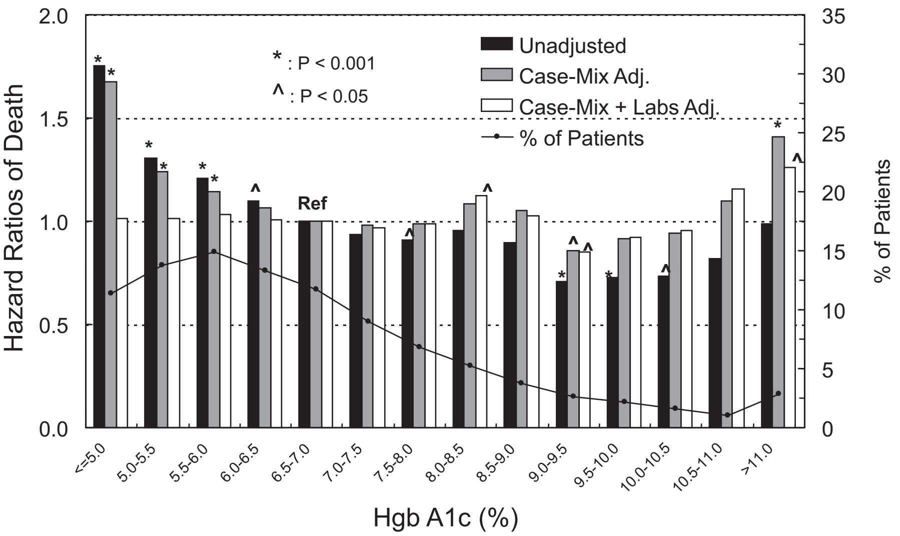

FIGURE 42.4 Relation of glycemic control and hemodialysis survival among 24,875 hemodialysis patients with follow-up of 3 years, using time-dependent survival models with repeated measures. Data were collected at baseline and every quarter to a maximum of 3 years' follow-up. Extremes of glycemia were weakly associated with survival in the study population [62].

that the overall relationships between glycemic control and survival outcomes are weaker in the presence of ESRD (Fig. 42.4). The use of higher HbA1c targets than for the general diabetes population appears to be preferable in patients with higher levels of comorbidity, according to KDOQI and kidney disease improving global outcomes (KDIGO) clinical practice guidelines [99]. In a large observational study of diabetic hemodialysis patients, only extremes of glycemia (HbA1c < 6.5% and >11%) were associated with increased death risk [64]. In a comparably large study with multiple adjustments, Kalantar-Zadeh et al. found that higher HbA1c levels were incrementally associated with higher mortality risk [63]. A smaller but more recent clinic-based study found no association of higher baseline HbA1c with risk of ESRD or death [100].

While many factors in ESRD may conspire to lower HbA1c values, which may only reach >6% in up to one-third of patients [63], some patients have been characterized as having a condition of "burnt-out diabetes," with spontaneous hypoglycemia and cessation of antidiabetic medications [101], and high risk for poor outcomes, including mortality. A recent study in chronic peritoneal dialysis patients reported that of those identified as "burnt-out diabetes" by HbA1c < 6% (21%), the number was reduced by half when a low GA (<16%) was added to the diagnostic criteria [102].

The validity of HbA1c relative to other metrics in ESRD, discussed previously, was evaluated in the GIDE study, which confirmed that HbA1c may be affected by factors not directly related to glycemic control [103]. Analysis of evidence linking serum GA to diabetic ESRD outcomes is now emerging. Freedman et al. [104] determined the association between GA, HbA1c, and serum glucose levels with outcomes (hospitalization, survival) in diabetic dialysis patients (90% hemodialysis) (Fig. 42.5). Quarterly serum GA levels were measured for up to 2.3 years in 444 prevalent patients. Time-dependent analyses allowed comparisons with available HbA1c and monthly random serum glucose levels. Mean (SD) serum GA was 21.5 ± 6% and HbA1c was 6.9 ± 1.6%. Increasing GA, but not HbA1c or serum glucose concentrations were predictive of hospitalization and survival. In a large study of 84,282 patients with prevalent diabetes on maintenance hemodialysis, about one-quarter had both GA and HbA1c values [105]. One-year mortality was determined using a Cox regression analysis. Results indicated the superiority of GA over HbA1c in predicting mortality. A recent 2-year nationwide cohort study from Japan in 1601 peritoneal dialysis patients with prevalent diabetes found an association of GA levels >20% and decreased survival, but no association involving HbA1c levels [106].

Hypoglycemia

Increasing and revived attention is being given to the perils of hypoglycemia (<70 mg%) in the diabetic CKD/ESRD population. The American Diabetes Association recommends a goal HbA1c of <7.0% or as close to normal and as safely as possible without unacceptable hypoglycemia [2]. However, diabetes itself is characterized by acute glucose fluctuations and general glycemic variability (GV). Therefore the regimens used for serum glucose control should be associated with a low risk of hypoglycemia. However, with increasing pressure to achieve tight glycemic control targets, hypoglycemia, in many cases iatrogenic, is becoming more prevalent. In general, the use of insulin secretagogues, missed meals, advanced age, duration of diabetes, and unawareness of hypoglycemia are

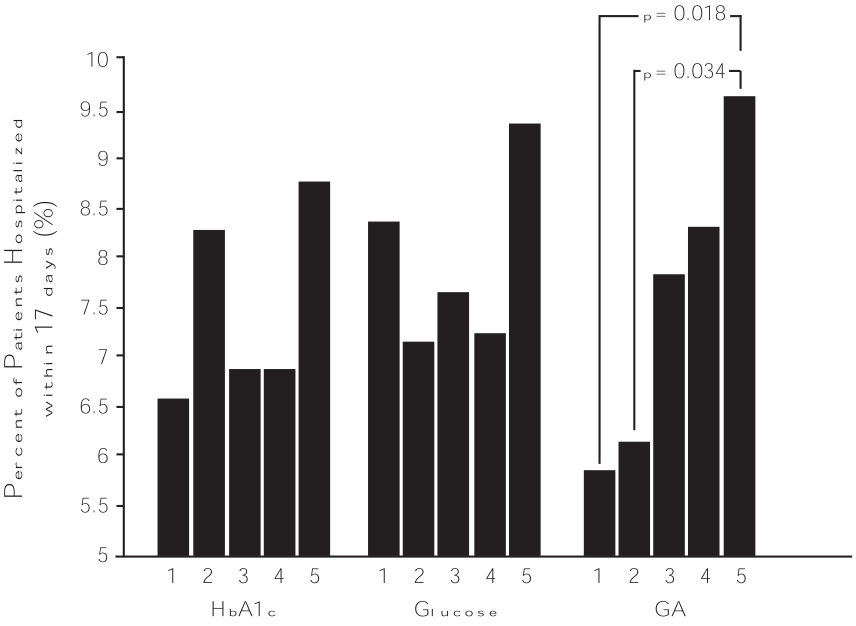

FIGURE 42.5 Relationship between longitudinal measurements of glycated albumin levels and hospitalization rates within 17 days of the measurement in 444 patients with ESRD and diabetes. Higher glycated albumin rates were increased hospitalization and also with poorer survival (not shown) [104]. *ESRD*, End-stage renal disease.

factors that increase the risk of hypoglycemia [107]. Although hypoglycemia is associated with more intensive glycemic therapy and causes adverse clinical outcomes in patients with diabetes, published reviews on glycemic control in diabetic CKD patients typically include only token mention of hypoglycemia [13]. Increasing attention is being given to the risks of hypoglycemia (below the fasting reference range of about 70 mg/dL) in the diabetic CKD/ESRD population. The altered glucose metabolism in CKD patients poses not only a problem for blood glucose control but also increases the risk of hypoglycemia, which may occur in both diabetic and nondiabetic CKD patients, and which then becomes a deterrent to achieving glycemic control at current target levels for patients with diabetes. The greatest risk of harm is in patients with both CKD and diabetes, particularly in the elderly [108], in whom hypoglycemic episodes may be difficult to diagnose. A large recent population-based study from Taiwan reported a hazard risk of hypoglycemia for CKD in patients with type 2 diabetes of 1.77 [109]. A number of recent reports indicating increased mortality in patients receiving intensive glycemic therapy has driven the renewed interest in hypoglycemia as a marker of adverse clinical outcomes [110]. In settings such acute myocardial infarction [111] or the intensive care unit [112], enthusiasm for aggressive glycemic control has been tempered by its association with hypoglycemia and worse outcomes. Recent large studies have shown a lack of benefit and sometimes higher risks of morbidity and mortality with tight intensive glycemic control [113], pointing the way toward less intensive glycemic control in at-risk populations Adverse consequences of hypoglycemia could partially explain the outcomes from three recent studies, Action to Control Cardiovascular Risk in Diabetes (ACCORD) [114], ADVANCE [115], and veterans administration diabetes trial (VADT) [116], which tried to determine whether diabetes management more aggressive than currently recommended (with a goal of achieving HbA1c levels near 6.0%) would reduce cardiovascular risk in patients with long-standing diabetes. Hypoglycemia occurred more frequently in the intensive therapy arms of all three trials, and in the ACCORD trial, the rate of hypoglycemic episodes requiring medical assistance was three times higher. In ADVANCE, severe hypoglycemia was nearly twice as common in the intensive control group, and half of patients in the low A1c group had at least a minor hypoglycemic event during the study. All three trials failed to demonstrate cardiovascular benefit with such intensive therapy. The ACCORD trial had significantly greater mortality in the intensively treated group and was terminated early because of this higher mortality. This latter group also suffered more hypoglycemia. However, the greater frequency of hypoglycemia in the intensive treatment group was not considered to be the likely explanation for their excess mortality. A subsequent analysis of the ADVANCE trial indicated that severe hypoglycemia constituted an independent cardiovascular risk factor, that is, was associated with increased macrovascular events and death from a cardiovascular cause [117]. Reports on hypoglycemia and kidney disease have generally been limited to case reports, small series, and reviews [118]. In the ADVANCE trial analysis, higher creatinine levels were an independent risk factor for severe hypoglycemia [117]. In patients with uremia, hypoglycemia is more common than generally appreciated. ESRD unrelated to diabetes is the second most frequent cause of hypoglycemia in hospitalized patients [118] and has a high mortality rate [119]. However, concomitant illness, malnutrition, or drugs commonly contribute to hypoglycemia in these patients [120]. Only one-half of the cases of renal insufficiency and hypoglycemia were diabetic in one study [121]. Mild cognitive impairment, a common problem, particularly in the elderly ESRD patient, may predispose patients to hypoglycemia. In diabetic ESRD patients, glucose levels may be lower during the intradialytic period, and the risk of hypoglycemia is greater during the first 24 hours after a hemodialysis treatment [122].

Epidemiological data regarding the incidence of hypoglycemia among CKD/ESRD patients and on the association between hypoglycemia and overall clinical outcomes have increased in recent years [123]. In one survey, one-half of diabetic chronic hemodialysis patients suffered hypoglycemia over a 3-month period [124]. In a recent CKD report the rate of hypoglycemia within diabetes strata was higher in subjects with CKD, and the risk of severe hypoglycemic events was highest in the group with both diabetes and CKD [122], being roughly twice as high in patients with diabetes who also had CKD versus those who did not. In a recent cross-sectional analysis of adverse events associable with CKD in a large sample size of hospitalized patients with CKD stages 1–4, 2% were due to hypoglycemia [125]. Of note, another recent report using continuous glucose monitoring (CGM) in a modest type 2 diabetes cohort of participants with CKD compared to those without CKD confirmed that hypoglycemia was common but failed to demonstrate a heightened risk related to CKD [126]. The authors concluded that milder hypoglycemia episodes detectable with CGM may not be more frequent related to CKD, but that CKD could increase the likelihood that more severe, clinically apparent episodes are more likely in patients with CKD, as supported by other studies not utilizing CGM.

Aggressive glycemic control in hospitalized patients with CKD may also be associated with increased risk of hypoglycemia without overall improvement in outcomes [127]. A recent report performed a retrospective propensity-matched analysis of patients with diabetes with or without AKI during hospitalization, using a national cohort of US veterans, to determine whether an acute kidney injury (AKI) episode increased risk for subsequent hypoglycemia [128]. After adjustment, AKI was associated with a 27% increased risk of hypoglycemia over 3 months after discharge and varied from 18% (if full renal recovery) to 48% (if no renal recovery).

TABLE 42.1 Factors contributing to hypoglycemia.

- Poor caloric intake
- Impaired hepatic glycogenolysis
- Defective renal gluconeogenesis
- Diminished counterregulatory response
- Increased glucose variability
- Medications

The pathogenesis of hypoglycemia in diabetic CKD patients is complex and coexists with overall disturbances of glucose metabolism in renal failure. As with uremic carbohydrate intolerance, several factors in CKD/ESRD may promote "renal hypoglycemia" (Table 42.1). Anorexia and suboptimal caloric intake lead to reduced glycogen stores. Reduced renal insulin clearance as the GFR falls to 15–20 mL/min/1.73 m^2 results in a prolonged action of insulin. The kidneys are the most important extrahepatic organs for degradation of insulin, and their contribution to insulin removal decreases with declining kidney function. However, insulin levels generally are reported as normal when measured [129]. Insulin, sulfonylureas, and meglitinides are the diabetic agents most likely to be associated with hypoglycemia in the setting of CKD/ESRD. Oral antidiabetic therapies that are renally excreted frequently contribute to hypoglycemia. Insulin doses often need to be reduced by as much as half, especially after dialysis has been initiated, to avoid hypoglycemia. Rapid-acting insulin analogs may be less likely to cause hypoglycemia than regular insulin because the pharmacokinetics are less effected by renal failure [130]. Improved insulin sensitivity may contribute to posthemodialysis hypoglycemia [110]. In addition, the incidence of hypoglycemia may be lower with basal insulin analogs compared to intermediate-acting agents [131], although more sustained if it does occur. The decline in renal mass and impaired kidney function lead to decreased renal gluconeogenesis. During starvation the kidneys become a major source of glucose production through gluconeogenesis from precursor molecules. Deficient catecholamine release in renal failure leads to an impaired counterregulatory response that would normally defend against hypoglycemia. The protective response of glucagon, epinephrine, cortisol, and growth hormone is known to be impaired in DM [132], and deficiencies in glucagon and catecholamines are known to occur in uremic diabetic patients [133]. A case report supported a role for parathyroid hormone in inhibiting insulin secretion in a nondiabetic chronic hemodialysis patient; severe hypoglycemia with endogenous hyperinsulinemia followed parathyroidectomy for severe secondary hyperparathyroidism [134]. Nosocomial hypoglycemia may also occur due to administration of any one of a number of other medications, including β-adrenergic blockers, salicylates, propoxyphene, and sulfonamides [135]. The risk of hypoglycemia may be increased in type 2 patients on sulfonylureas who are treated with antimicrobial agents of various categories [136], for unclear reasons. Preliminary findings suggest that the risk of hypoglycemia is especially high in diabetic ESRD patients who have greater glycemic variability [137].

As noted previously, the health consequences of hypoglycemia can be severe. Glucose is a required fuel for the brain under physiological conditions. Hypoglycemic unawareness may occur. Signs and symptoms, when they do occur, include cold sweats, agitation, dizziness, disorientation, slurred speech, fatigue, altered mental status, including decreased level of consciousness, and seizures. Increased stroke risk may also occur [138]. The occurrence of hypoglycemia complicated by central pontine myelinolysis and quadriplegia has been described [139]. Hypoglycemia, particularly when severe, is a powerful stimulant to the sympathetic nervous system and may cause acute secondary adverse cardiovascular outcomes. The adrenergic response may result in chest pain due to coronary vasoconstriction and ischemia, myocardial infarction, serious cardiac arrhythmias, including QT prolongation and ventricular arrhythmias, and sudden death [140]. While the DCCT clinical trial showed no adverse effects of intensive therapy, without or with severe hypoglycemia, on cognitive status measured objectively over 18 years of follow-up [141], a recent study among elderly type 2 patients with no prior cognitive impairment showed that episodes of hypoglycemia may be associated with increased risk of dementia [142]. The heightened risk of hypoglycemia in the interval before initiation of dialysis, and its effect on outcomes in diabetes patients with declining kidney function transitioning to ESRD was addressed in a recent report [143]. Among 30,156 patients with diabetes and CKD who developed ESRD, the occurrence of pre-ESRD hypoglycemia-related hospitalizations using Cox regression models adjusted for case-mix covariates was associated with higher post-ESRD mortality (hazard ratio (HR) = 1.25), and more frequent episodes had incrementally higher mortality risk.

GV, a measure of volatile glycemic control, is not only a well-established risk factor for hypoglycemia but is increasingly associated with higher independent risk of diabetes-related complications, including mortality. Of note, glucose variability and severe hypoglycemia in ESRD may be associated with higher, not lower, HbA1c values [144]. The use of CGM has led to various operational definitions of GV. These range from basic indices, such as glucose standard deviation, to more complex ones such as mean amplitude of glycemic excursions (MAGE) (the arithmetic mean of the more extreme glycemic excursions) [145]. A recent report utilizing CGM brought attention to the unique problems of GV in acutely ill dialysis patients with diabetes who were hospitalized [146]. The use of a closed-loop insulin-delivery system resulted in superior glycemic control, including less GV and less hypoglycemia. However, the device requires more thorough validation in this patient population [147].

Diabetes/bone and mineral metabolism

Epidemiologic evidence and prospective studies have linked vitamin D deficiency to an increased risk of diverse chronic diseases, including autoimmune and cardiovascular disease, cancer, infectious diseases, and type 2 DM [148]. Epidemiologic data also suggest that a significant proportion of cases of type 2 diabetes (the most common form of diabetes) may be attributed to modifiable risk factors related to lifestyle and personal habits [149]. Diabetes is a risk factor for bone loss [150]. Diabetes directly impairs osteoblast function which may lead to decreased bone mass and suppression of bone turnover and impairs bone quality by blunting the secretion of parathyroid hormone. Diabetes also modifies bone collagen through advanced glycation endproducts (AGE) modification [151,152]. Even when bone density in diabetics appears to be similar to that of nondiabetics, diabetic bone may be more fragile [153].

Vitamin D deficiency and insufficiency have been defined as a serum 25-hydroxyvitamin D <20 ng/mL and 21–29 ng/mL, respectively [148]. Data indicate that patients with diabetes have lower serum concentrations of vitamin D than other patients, [154] as well as lower serum intact parathyroid hormone levels [155]. There is little information regarding why DM is associated with low serum vitamin D levels. Recent animal and human studies have provided confirmation that vitamin D might be a potential risk modifier for diabetes [156]; that is, there may be an association between diabetes and vitamin D deficiency. A meta-analysis of five observational studies of vitamin D supplementation in children reported a nearly one-third risk reduction of type 1 diabetes in children who reported ever having received vitamin D supplements [157]. In one study, a low vitamin D status doubled the risk of newly diagnosed type 2 diabetes in elderly patients, after multiple statistical adjustments [158]. An inverse association between vitamin D status and both type 1 and type 2 diabetes has been suggested by some observational studies, whereas other studies on this subject are inconclusive. Based on published data that vitamin D deficiency is associated with impaired B-cell function and IR in animal models and humans, Mattilo et al. evaluated longitudinal data from 4097 adults collected from 1978–80 as part of the Mini-Finland Health Survey [159]. The relative risk of type 2 diabetes between quartiles of vitamin D, after adjustment for confounding factors, was estimated using Cox's model. A significant inverse association was determined between serum 25-OH-D levels and the risk of type 2 diabetes.

To evaluate the association of HbA1c levels with vitamin D status in US adults, Kositsawat et al. analyzed data on 9773 participants in the NHANES 2003−06 [160]. After adjustment for multiple covariates, they observed an inverse relationship between A1c and 25-(OH)-D levels in those individuals who were 35−74 years old. Limited by a single determination of both A1c and vitamin D levels, these cross-sectional results nonetheless suggest a metabolic link between vitamin D concentrations and glucose homeostasis. The authors suggest screening patients with elevated A1c levels for vitamin D deficiency. Data that relate vitamin D and the risk of type 2 diabetes are limited by post hoc analyses and generally inadequate adjustment for confounding variables [161]. The mechanisms by which vitamin D deficiency may cause DM could include increased IR, decreased insulin secretion, and/or autoimmune/inflammatory damage to pancreatic islet cells [156]. A vitamin D receptor and expressible 1-alpha-hydroxylase are present in pancreatic beta cells. Potential mechanisms whereby vitamin D might affect glucose metabolism by enhancing insulin sensitivity have been recently reviewed [156]. Vitamin D is thought to have both direct (through activation of the vitamin D receptor) and indirect (via regulation of calcium homeostasis) effects on several mechanisms relevant to glucose homeostasis, which could enhance the risk for diabetes in the presence of vitamin D deficiency. A study examined vitamin D status and the relationship between serum 25-(OH)-D concentrations and the components of IR. Insulin sensitivity/resistance was calculated by the quantitative insulin sensitivity check index. Only 17% of subjects had serum 25-(OH)-D concentrations in the recommended range of ≥30 ng/mL. IR was significantly and inversely correlated with serum vitamin D concentrations [162]. Vitamin D status and IR (by HOMA-IR) were also inversely related in the data obtained from the NHANES III [163]. Although correcting and preventing vitamin D deficiency might have beneficial effects on diabetes and CKD, few prospective trials have been conducted to determine the effects of vitamin D supplementation on IR in CKD patients [164]. Of interest is a placebo controlled 6-month trial of vitamin D3 of 96 participants (randomized, placebo-controlled) with type 2 DM who underwent hyperinsulinemic−euglycemic clamp. The participants on vitamin D had improved peripheral IR and β-cell function [165]. These results suggest that vitamin D3 could improve glycemic control in type 2 DM.

In contrast to observational studies, information pooled from vitamin D interventional trials for the most part appear to be inconclusive [166]. Might vitamin D have a role in reducing the risk of diabetes? The Women's Health Study, for example, suggested a reduction in the development of type 2 diabetes related to a modest increase in vitamin D intake but lacked statistical adjustments [167]. Small doses of vitamin D do not appear to affect measurements of fasting glucose or IR. Vitamin D supplementation in pregnancy or early childhood may reduce the subsequent risk of type 1 diabetes [156]. In one study, Marjamaki et al. reported data from the Diabetes Prediction and Prevention Study, in which the dietary habits of Finnish women were carefully examined and linked to the onset of autoimmunity in their offspring [167]. There was no correlation between the amount of vitamin D consumed by the mother and the appearance of islet autoantibodies in the blood of their offspring in the first postnatal year. Longitudinal observational studies suggest an inconsistent association between vitamin D insufficiency and incident type 2 diabetes [156]. Studies addressing administration of high doses of vitamin D or metabolites with diabetes had been limited to trials involving small numbers of patients or animal studies until recently [168]. An important study published in the New England Journal of Medicine in 2019 did address the question as to whether high doses of vitamin D3 would prevent the development of type 2 diabetes [169]. The study enrolled patients thought to be at high risk for the development of type 2 DM and randomized them to 4000 IU/day of vitamin D3—cholecalciferol (2423 participants) or placebo (1211 participants) regardless of their baseline vitamin D level. After a mean follow-up of 2.5 years, there was no prevention effect observed. Perhaps, people with very low levels of vitamin D might have a preventative effect (the average baseline was about 28 ng/mL and rose to 54.3 ng/mL in the treatment group), but routine supplementation for the prevention of type 2 DM cannot be supported at this time.

The active metabolite of vitamin D regulates transcription of multiple gene products, with antiproliferative, prodifferentiative, and immunomodulatory effects. For example, in vitro studies of bone marrow red cell precursor cells demonstrated that 1,25-vitamin D increases Epo-receptor expression [170]. One recent study showed that both 25-vitamin D and 1,25-vitamin D deficiency are associated with anemia [171]. In a study from Denmark, severe vitamin D deficiency was associated with increased all-cause (HR 1.96) and cardiovascular (HR 1.95) mortality [172] in patients with diabetes. Diabetes itself is known to disturb bone metabolism, chiefly in the form of low bone turnover [173], although the relationship between diabetes and bone disease is complex [153]. Both type 1 and type 2 diabetes are associated with increased bone fragility and a higher risk of fracture. Abnormalities in a number of regulators of bone metabolism have been demonstrated in diabetes that might play a role in the genesis of diabetes-associated osteopenia and reduced osteoblast function. Such abnormalities may include altered vitamin D regulation and relatively low serum parathyroid hormone levels. In cultured bovine parathyroid cells, for example, high glucose levels reversibly suppress parathyroid secretion [174]. Changes in osteoblast phenotype were demonstrated in one recent study, where decreased matrix mineralization was described in bone marrow culture from diabetic mice [175]; this was associated with decreased gene expression of osteocalcin, parathyroid-related protein receptor, the parathyroid receptor, and other factors.

Several studies have demonstrated that calcitriol, paricalcitol, and 1-alpha-D2 effectively suppress serum parathyroid hormone (PTH) levels [176]. Tanaka et al. evaluated the impact of diabetes on vitamin D metabolism in predialysis CKD patients by extracting data from over 600 patients (112 of whom had diabetes) in the observational Osaka Vitamin D study [152]. The study reported differences in relevant laboratory measurements (intact parathyroid hormone, 25-hydroxyvitamin D, calcitriol, fibroblast growth factor-23 (FGF-23), calcium, and phosphorus) between 112 diabetic and 112 nondiabetic patients matched for gender, age, and eGFR. Bone mineral density and urinary protein excretion were also determined. No enrolled patient had received vitamin D, bisphosphonates, estrogens, or raloxifene. Mean eGFR was 34.6 mL/min/1.73 m^2 in the diabetic group and 35.6 mL/min/1.73 m in the controls. Corrected serum calcium and serum phosphorus were slightly higher in the diabetes group, while neither PTH nor FGF-23 differed; serum levels of both of these latter hormones increased as kidney function declined. However, diabetic patients had more deficient vitamin D status. Despite similar levels of serum PTH, the diabetes group had lower serum 1,25-D (calcitriol) levels ($P < .0001$) (Fig. 42.6); this difference persisted after multivariate linear regression adjustments for the degree of proteinuria. Low 1,25-D levels in diabetes were related to lower levels of 25-D, its substrate. In diabetic dialysis patients, osteodystrophy is mainly manifested as an aplastic or low turnover type due to low serum intact PTH concentrations. Several vitamin D analogues are available for treatment in CKD patients [177]. Serum PTH levels were affected by the degree of glycemic control in one hemodialysis study, with lower PTH levels in those with poor glycemic control [178]. There are currently no data indicating that the needs for other vitamins or for trace elements for the patient with diabetic CKD are different from that of CKD patients without diabetic kidney disease who have the same degree of proteinuria.

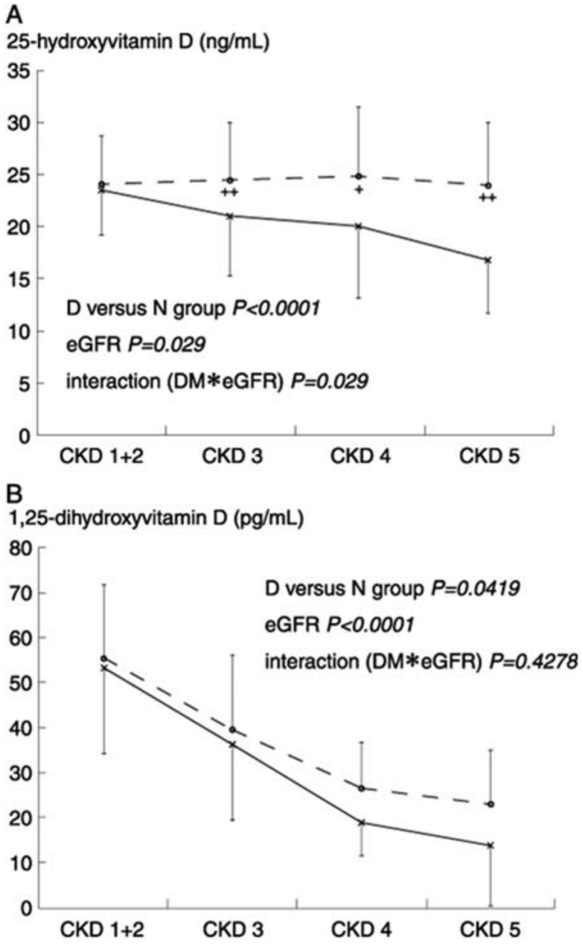

FIGURE 42.6 Impact of diabetes and CKD on vitamin D status in predialysis patients. Differences between the groups were observed in the association between CKD stage and both 25-hydroxy- and 1,25-hydroxyvitamin D. Broken line = nondiabetic, solid line = diabetic. Compared with nondiabetics, diabetic CKD patients had poorer vitamin D status [152]. *CKD*, Chronic kidney disease.

Dietary protein intake and diabetic kidney disease

Dietary protein intake has been considered to be an important factor in maintaining kidney health since the last half of the 19th century. There have been many low-protein diets proposed for CKD patients that, initially, were usually aimed at limiting the symptoms of patients with near ESRD and/or reducing the effects of azotemia. Some of the early studies were also designed to reduce progression of CKD. An article by Giordano in Kidney International [179] described the work in 1923 of F.M. Allen at the New England Deaconess Hospital. Dr. Allen did studies to determine the feasibility of a very-low-protein diet initially by feeding a medical student a diet of 4000 calories for 24 days that consisted of carbohydrates and fats (and only 300 mg of protein/day). The urine urea nitrogen excretion dropped from 14.25 to 1.58 g/day. Apparently, the medical student stopped the study earlier than Dr. Allen because the student feared for his health and had distaste for the very-low-protein diet. Dr. Allen followed up that study by administering a diet of 18 grams of protein/day to a 70-kg azotemic patient (0.26 g/kg) for 6 months. The diet successfully lowered nitrogen waste excretion but was extremely hard to maintain.

The contemporary approach to the utility of low-protein diets derives primarily from work from the 1970s to 1990s. Low-protein diets have been used for two major goals: (1) to slow the decline in GFR and (2) to ameliorate signs and symptoms of patients with near ESRD. But are low-protein diets effective? Seminal work from this time period was done in Munich-Wistar rats that have their glomeruli near the cortical surface thus making them accessible for micropuncture studies [179–185]. Using tiny glass pipettes, researchers measured glomerular pressures (including transcapillary pressure, ΔP) and GFR as well as afferent renal blood flow, Q_A). The value of this animal model is that very exact, detailed readings could be obtained from single nephrons. As most models of kidney failure take a long time to develop, rat models were designed to accelerate the rate of decline in GFR. These models included various degrees of removal of kidney tissue such as the one and two-thirds nephrectomy model where the rat was left with only one-third of one kidney. Other models consisted of altering the protein in the diet and/or making the animals diabetic.

A landmark paper published by Zatz et al. provided a hemodynamic explanation for declining GFR and a pathophysiologic rationale for limiting protein in the diet in patients with diabetic kidney disease [185]. Rats were maintained for 1 year on a 6% protein diet (low protein), 12% protein diet (normal rat diet), or 50% protein diet (high protein). In addition, half of the rats were made diabetic. Rats were studied at 2–10 weeks for micropuncture studies and at 11–13 months for pathology. Fig. 42.7 shows the essential findings that as protein intake increased there were increases in single-nephron GFR (SNGFR) and increases in Q_A and ΔP. Animals that were diabetic had even greater increases in SNGFR, Q_A, and ΔP. And the combination of a high-protein diet and diabetes engendered the greatest increase in all of these parameters. Importantly, the rats maintained on the low-protein diet (diabetic or not diabetic) showed no changes in these parameters as compared to nondiabetic control rats on a normal 12% diet. Urinary albumin excretion was also studied. The data revealed that the diabetic rats fed a high-protein diet developed especially high levels of urinary albumin, whereas the rats fed the low-protein diet had normal levels of urinary albumin, whether or not they were diabetic (Fig. 42.8). Examination of the kidney pathology consistently revealed a lesion of secondary focal and segmental sclerosis in the rats that had increased glomerular pressures, blood flow, and increased urine albumin levels as compared to the rats with normal glomerular pressures and blood flow. Thus the hypothesis for progression of diabetic kidney disease was proposed, stating that glomerular hyperfiltration/hypertension leads to progressive sclerosis of glomeruli and loss of GFR and interventions that prevent these hemodynamic changes should slow or prevent the decline in GFR. Hence, low-protein diets should effectively slow progression by lowering intraglomerular pressures and blood flow rates. These

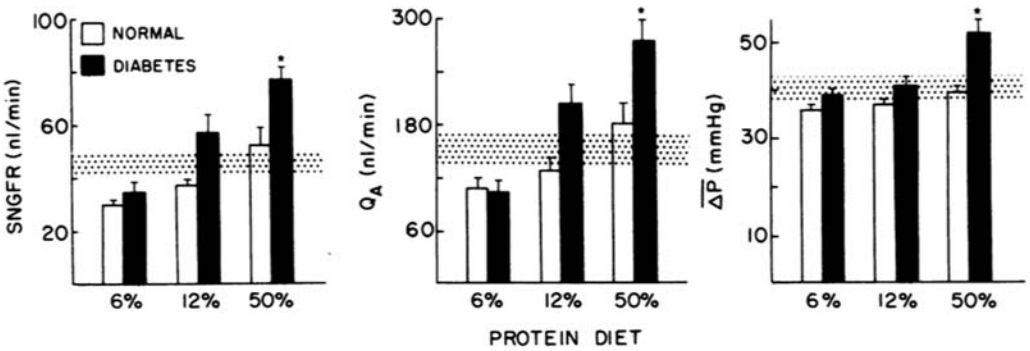

FIGURE 42.7 Munich-Wistar rats were treated with three different diets as noted previously and were either nondiabetic or diabetic (by injection of streptozotocin). After 2–10 weeks, micropuncture studies were performed. Both increased dietary protein and diabetes led to increased glomerular flow rates (SNGFR), afferent renal arteriole blood flow rate (Q_A), and intraglomerular pressure ($\Delta \Pi$). The combination of high protein and diabetes had the greatest increases in these hemodynamic parameters [186]. *SNGFR*, Single-nephron glomerular filtration rate.

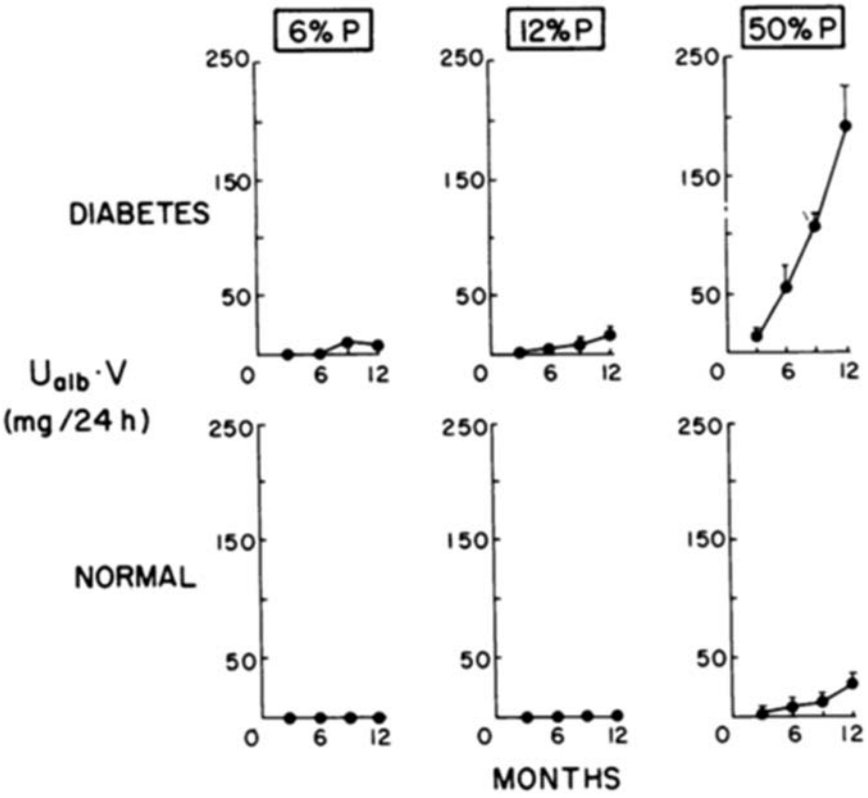

FIGURE 42.8 Munich-Wistar rats were treated with three different diets as noted previously and were either nondiabetic or diabetic (by injection of streptozotocin). Dietary protein percentages are shown at the top of the graph. Urinary albumin excretion rates were followed over time. The combination of diabetes and 50% protein diet had the greatest effect on increasing urinary albumin excretion rate [186].

results provided very compelling arguments for human studies to test the value of low-protein diets for slowing progression of diabetic kidney disease.

Although these physiological studies appear to be convincing, there are concerns as to the interpretation of results, which are as follows. First, the measurements in these models were from a very small number of nephrons and may not reflect hemodynamics in the kidney as a whole. Second, of necessity, the micropuncture studies were a snapshot in time and may reflect only the hemodynamics of that time period but not necessarily reflect the hemodynamics over an extended period of time. Indeed, the micropuncture measurements were done at 2–10 weeks after the creation of diabetes, whereas the increases in urine albumin level did not occur until months later. And the pathology was examined 10–12 months after the micropuncture studies. Moreover, these results indicate that glomerular hyperfiltration per se is deleterious; yet, to date, there is no convincing evidence in humans that prolonged glomerular hyperfiltration does predict declining GFR. Third, there is the usual concern that animal models do not reflect human disease, nor do they necessarily reflect the response to treatment in humans. Nevertheless, important studies such as Zatz et al. and others have provided the basis for the hypothesis that a critical component of treatment of patients with diabetic kidney disease is to lower the intraglomerular pressures or flows [179–185]. Hence, the presumed efficacy of low-protein diets is to lower intraglomerular pressures and flows. Since angiotensin II is the major regulator of intraglomerular pressures by causing vasoconstriction, preferentially in the efferent arteriole, studies have been conducted using inhibitors of angiotensin II. In a subsequent paper, Zatz et al. used the ACEI enalapril in the same diabetic rat model that the protein studies were done and showed that enalapril reduced glomerular pressures, lowered urine albuminuria, and ameliorated the deleterious effects of diabetes on rat kidneys [184]. Since then many human studies have proven that agents that block the actions of angiotensin II successfully slow progression of diabetic kidney disease in patients who have increased levels of urine albumin level. These medicines include the ACEIs, angiotensin receptor blockers, and renin inhibitors [186]. Interestingly, for these medicines there is evidence that there is a hemodynamically mediated decrease in GFR that is necessary for optimal efficacy of these agents. For example, in the reduction of endpoints in NIDDM with the angiotensin II antagonist losartan (RENAAL) study in which diabetic patients were treated with or without the ARB, losartan, the results demonstrated that the greater the initial decline in GFR in patients treated with losartan, the slower the subsequent rate of decline in GFR. [187–188]. Of note, these studies do not prove that decreases in GFR are mechanistically important for the effect of losartan for slowing the decrease in GFR; this reduction in the decline in GFR may just be a marker of drug effect.

Since the early 1980s there have been many small studies that suggested that low-protein diets were effective in slowing progression of diabetic kidney disease. However, the largest and most influential study on the effect of low-protein diets on the progression of kidney disease had very few diabetic kidney disease patients. The Modification of Diet in Renal Disease (MDRD) study that was published in 1994 [189] followed two groups (the mean follow-up was 2.2 years)—one with GFRs between 25 and 55 mL/min (585 participants—who were randomly assigned to a "normal" protein diet providing 1.3 g/kg/day or a low-protein diet containing 0.58 g/kg/day) and a second group with more advanced kidney disease who had GFRs between 13 and 24 mL/min (255 participants) and who were randomly assigned to diets providing either 0.58 or 0.26 g/kg/day (with supplementation with some essential amino acids and ketoacid analogs of other essential amino acids). The results did not show a beneficial effect of low-protein diets on slowing progression of renal disease. There was also a low versus normal blood pressure arm of this study. As has been shown by many studies, blood pressure control had a significant effect on slowing a decline in GFR. Only 3% of the participants had diabetes and all of these people had type 2 diabetes as the researchers excluded any patients who were taking insulin. Thus this study did not adequately determine whether diabetic kidney disease patients would have benefit from a low-protein diet. But the negative results of the MDRD led to much decreased enthusiasm for routine use of low-protein diets. In 1999 many of the authors of the original study wrote a retrospective review arguing that at best this study was inconclusive and that there were trends toward better outcomes in patients who were assigned to the low-protein diet [190]. Moreover, several problems were inadvertently incorporated into the experimental design of the MDRD study. These are discussed in Chapters and might account for the inconclusive results of this trial. Thus it has been argued that a low-protein diet should still be considered for patients with CKD. Interestingly, the achieved protein diet (as measured by 24-hour urine protein excretion) in the low-protein diet group (0.58 g/kg/day) was about 0.77 g/kg/day, almost the same as the recommended protein intake for diabetic patients by the American Diabetes Association of 0.8 g/kg/day [191]. So the argument as to whether diabetic kidney disease patients should be treated with a low-protein diet might well be a moot one. However, some workers in this field do recommend substantially lower protein diets for CKD patients.

In 1997 the EURODIAB IDDM trial was published [192]. In this study, 2696 type 1 diabetic patients in 30 countries had their dietary history taken and laboratory values measured. The results showed that patients who had <20% of their calories from protein had lower levels of urinary albumin excretion as compared to those patients who reported >20% of their calories from protein. The study appeared to show that as dietary protein increased there was a gradual and significant increase in urine albumin excretion. But the participants with higher urinary albumin excretion also had worse glucose control (as measured by higher glyco HbA1c) and higher blood pressure. In fact, the combination of increased A1c and increased blood pressure was the strongest predictor of high urinary albumin excretion rates, suggesting that protein intake was much less important. Another study published in 2007 from the ERIKA Study group evaluated three diets: very low protein (0.35 g/kg/day), low protein (0.6 g/kg/day), and a free diet (ad libitum protein intake) in patients with stages 4 and 5 CKD [193]. There was significantly lower urinary protein excretion in the very-low-protein diet group after 6 months of dietary treatment and not in the other two groups. But it was also noted that the salt intake (as measured by urine sodium content) decreased significantly as protein content in the diet decreased. This suggests the possibility that the decrease in dietary salt intake led to a decline in blood pressure as the main reason for the observed reduction in urine protein level. Indeed, the mean blood pressure in the very-low-protein group was 143/84 mmHg at the beginning of the study and decreased to 128/78 after 6 months. The authors concluded that factors other than the amount of protein ingested were responsible for the decrease in urine protein excretion. In 2009 the Cochrane Reviews performed a detailed analysis of randomized controlled trials in patients with diabetic kidney disease [194]. The authors' conclusions were that at that time there was little published evidence that low-protein diets were of benefit for CKD patients. The protein content of the low-protein diets in the reviewed studies was not very low, between 0.6 and 0.8 g/kg/day, and the sample size of the studies evaluated was often relatively small. Hence, it could be argued that this Cochrane Review of low-protein diets for diabetic CKD is not definitive.

None of the studies convincingly showed an effect of low-protein diet on slowing progression of kidney disease in patients with diabetic nephropathy. It is our conclusion that at this time there is no convincing evidence that a low-protein diet is of benefit in patients with diabetic kidney disease. As the current recommendation for dietary protein for diabetic patients is routinely in the 0.8–1.0 g/kg/day range, a low-protein diet needs to be less than this. There is not enough evidence for a beneficial effect of protein diets of <0.6 g/kg/day for diabetic patients with CKD, and many studies, including the MDRD study, suggest that it is difficult to maintain protein diets at 0.6 g/kg/day or lower. On the other hand, the data are insufficient to prove that low-protein diets do not retard progression of CKD. Thus for diabetic CKD patients who are willing to try protein intakes in the range of 0.6 g/kg/day or very-low-protein diets (about 0.3 g/kg/day) supplemented with ketoacid/essential amino acid mixtures, it can be argued that they should not be discouraged from doing so (please see Chapter).

Another issue is the adherence to a low-protein diet. A recent 2-year study from Italy showed that adherence to a low-protein diet can be relatively high [195]. A total of 422 participants with stages 3–5 CKD were enrolled. The baseline diet was 0.59 g/kg/day and 6 months later the average protein intake was 0.72 g/kg/day). Two-thirds of the participants were still on the diet with the main reason for dropout being dialysis or death. Quality of life measures showed that the participants were satisfied with the diet. An excellent editorial about the study [196]. notes that even though the diet was well tolerated, it needs to be individualized. That is, patients where malnutrition is a concern should not be placed on a low-protein diet. The risks clearly outweigh the benefits. The authors of the editorial also wrote an interesting overview of vegetarian diets and CKD [197]. They are clearly in favor of vegetarian diets as they seem to have similar benefits to low-protein diets in that a vegetarian diet may lead to lower blood pressure, less inflammation, and less oxidative stress. But there is very little evidence at this time that a vegetarian diet per se is renoprotective.

So does the source of the protein make a difference? There are only limited studies on this issue. For example, Knight et al. studied changes in estimated GFR in 1135 participants with GFR > 80 mL/min and in a second group of 489 participants with GFR between 55 and 80 mL/min from the Nurses' Health Study [198]. Only a small percentage of the subjects had diabetes. The groups were subdivided into protein intake that was primarily nondairy animal protein, dairy protein, or vegetable protein. The participants taking the vegetable protein had either no decline or the slowest decline in GFR as compared to the other groups. It is relevant that this study evaluated dietary intake of protein only twice via questionnaires, in 1990 and 1994. Thus the reliability of the findings is brought into question by the limited frequency of data measurements in the same subjects. Another study (albeit one with only 300 patients) examined whether eating primarily fish protein was beneficial [199]. The authors noted that a high intake of fish protein significantly slowed the development of microalbuminuria in type 1 diabetic patients. These results are interesting but in and of themselves do not present a clear diet plan that should be prescribed for patients with diabetic kidney disease.

Lastly, the onset of end-stage kidney disease significantly changes the protein intake recommendations. Protein-energy wasting is a well-documented, important issue in dialysis patients that needs to be properly assessed and treated to prevent significant malnutrition. National Kidney Foundation guidelines recommend an intake of 1.2 g/kg/day for hemodialysis patients and 1.3 g/kg/day for peritoneal dialysis patients [200]. The recommendations for protein intake are higher in dialysis patients than nondialysis patients due to a combination of such factors as increased catabolic rates in dialysis patients, removal of nutrients during dialysis, effects of bioincompatible materials, and others [201]. Moreover, there is a close association of protein wasting with inflammation, strongly suggesting that proper protein intake is needed to limit the inflammatory state of dialysis patients [202]. An interesting retrospective analysis of 53,933 patients undergoing maintenance hemodialysis examined the relationship of mortality and protein intake by evaluating the relation between urea kinetic-based normalized protein nitrogen appearance and all-cause and cardiovascular mortality over a 2-year period [203]. Dialysis patients who ingested <0.8 or >1.4 g/kg/day had significantly higher mortality rates. The best survival was associated with a protein intake of 1.0–1.4 g/kg/day. The risks of protein and energy wasting are more pronounced in patients who also have diabetes possibly due to the effects of diabetes on metabolism, decreased effects of insulin, and/or IR as well as to comorbid conditions such as hypertension and vascular disease [204]. Hence, when diabetic patients approach end-stage kidney disease (at CKD stage 5), nutritional assessment should be conducted to provide optimal protein and calorie intake to prevent wasting and reduce inflammation.

Salt intake and diabetic kidney disease

The link between salt intake and hypertension has been established over many years of research. There is no question that in patients who are salt-sensitive, limiting salt intake will lead to lower blood pressure and as a result improved long-term outcomes (please also see Chapter). A 2010 Cochrane Review evaluated 818 studies related to reducing salt intake and progression of diabetic nephropathy and concluded that there was strong evidence for limiting sodium chloride intake to at least less than 5–6 g/day [205]. But the authors noted that there are relatively few well-controlled studies that specifically target salt intake independently of other variables, and that many studies are of short duration or use wide variations in sodium intake. Nevertheless, the current recommendation is to limit sodium chloride intake to help lower blood pressure, as lower blood pressure is clearly beneficial in slowing or even preventing progression of CKD. Moreover, salt intake needs to be limited in patients taking diuretics or the effect of the diuretic will be greatly diminished.

But is there a unique role for salt intake in the progression of diabetic kidney disease? It has been well established that diabetic kidney disease is associated with activation of the renin–angiotensin–aldosterone system (RAAS) [206,207]. Elevated levels of angiotensin II will lead to enhanced proximal reabsorption of sodium and elevated levels of aldosterone will lead to enhance collecting duct reabsorption of sodium. There are very few studies addressing the role of limiting salt intake in patients on specific medications. For example, Bakris and Smith evaluated the role of sodium intake on albumin excretion in diabetic nephropathy patients taking either the dihydropyridine calcium channel blocker, nifedipine, or the nondihydropyridine calcium channel blocker, diltiazem [208]. As previously observed, diltiazem led to a decrease in urinary albumin excretion whereas nifedipine did not. And a lower sodium chloride intake enhanced the effects of diltiazem on lowering the urinary albumin excretion. A similar study was done in patients who were treated with the angiotensin receptor blocker, losartan [209]. The authors reported that the achieved mean urinary sodium excretion on a low-sodium diet was 85 and 80 mmol/day in the losartan and placebo groups, respectively. In the losartan group the additional blood pressure–lowering effects when patients ingested a low-sodium diet, as compared to a regular sodium diet, for 24-hour systolic, diastolic, and mean arterial blood pressures were 9.7, 5.5, and 7.3 mmHg, respectively. In the losartan group the urinary albumin to creatinine ratio decreased significantly on the low-sodium diet as compared to the regular-sodium diet, and it was strongly associated with a decrease in blood pressure. These studies are illustrative of other reports in the literature. A more recent small study (89 participants with diabetic kidney disease) from Holland showed that a very low salt intake (average 393 mg/day) was effective in lowering blood pressure and albuminuria by enhancing the effects of RAAS inhibitors [210]. And a recent metaanalysis of salt intake and CKD also supported the use of at least moderate salt restriction [211]. An interesting study from South Korea though evaluated salt intake in incident CKD patients [211] and found that both high (> 4.03 g/day) and low salt intake (<2.08 g/day)was associated with worse outcomes (development of incident CKD as defined as an eGFR < 60 mL/min). But this association was only seen in participants with hypertension. This study is interesting as it included about 8000 participants over a 10- to 12-year follow-up. About 20% had diabetes. It is not clear if this study is generalizable. But it certainly is another example that dietary intervention always needs to be individualized. At this time though, the recommendation is that for hypertensive patients with diabetic kidney disease, it is prudent to limit salt in the diet to lower blood pressure, to enhance the effects of various antihypertensive and diuretic medications, and to improve cardiac outcomes [212].

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CHAPTER

43

Fructose: a lipogenic nutrient implicated in metabolic syndrome and chronic kidney disease

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Fructose is a simple sugar that is the primary nutrient in fruits and honey, which are classically considered healthy foods. Fructose is also a major component of refined sugar, which has classically been viewed as a nonnutritional food or "empty calorie." In the last decades the viewpoint that fructose is simply a caloric source of nutrition has shifted to one that places it at the top of the list for driving diseases such as obesity and diabetes. The new studies have raised important questions related to the optimal diet for subjects with chronic or end-stage kidney disease, in which historic recommendations focused primarily on a restriction of proteins (especially red meats) and high-fat diets. Here we both review the role of fructose in the subject with chronic kidney disease (CKD) and also make recommendations for management.

Sources of fructose

Fructose is the primary nutrient in fruits and honey and is responsible for its sweet taste. While this was the main dietary source of fructose for most of human history, the introduction of refined sugar from sugarcane, sugar beets, and palm trees led to a major increase in fructose intake, as sugar consists of a disaccharide of fructose and glucose. The intake of sugar rocketed from around 3 pounds per capita per year in 1700 to more than 150 pounds in 2000. Refined sugar caused a massive increase in the intake of sweets and desserts and was also commonly added to alcohol and other foods, with its largest source being soft drinks.

One problem with sugar is that it crystallizes easily, making it difficult to mix with many foods. A solution occurred in the 1970s when high-fructose corn syrup (HFCS) was introduced. Corn contains primarily dextrose (glucose), but a method was developed to convert glucose to fructose using an isomerase enzyme. This allowed a cheap source of fructose that could then be mixed with glucose as a combination of free monosaccharides, often containing 55% fructose and 45% glucose, which was found to be an optimal taste that consumers like. Advantages of HFCS include less crystallization at lower temperature, which is useful for frozen food such as ice cream, and an improvement of product flavor with browning development under heat in the Maillard reaction, in which fructose nonenzymatically binds to damaged lipids, protein, and DNA.

While sugar and HFCS are the primary sugars added to soft drinks and desserts, they are also often added to other foods. Today about 70% of processed foods contain these added sugars, and they are also a principal ingredient in most baby foods [1,2]. Currently, sugar represents approximately 15% of the normal diet, and in some groups (adolescents and ethnic minorities) the intake of sugar may reach 25% or more [3]. Importantly, trends are changing, and since 2008, there has been a progressive decrease in the intake of soft drinks containing sugar, although this has been countered to some extent by intake of sports drinks, energy drinks, and other sugary beverages [4].

Unfortunately, we are not only obtaining fructose from our diet. While dietary fructose is likely our primary source of fructose, fructose can also be endogenously

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TABLE 43.1 Conditions that stimulate endogenous fructose production.

Mechanism	Associated conditions
Elevated serum osmolality	Diabetes
	Dehydration
	High-salt diet
Hypoxia and ischemia	Myocardial infarction
	Ischemic organs
	Acute kidney injury
Dietary fructose (positive feedback)	High sugar diet
Hyperuricemia (positive feedback)	Metabolic syndrome
	Gout

produced under several conditions (Table 43.1). The sole mechanism for generating fructose in humans is via activation of the polyol pathway that converts glucose to fructose by sequential enzyme reactions, beginning with aldose reductase that converts glucose to sorbitol, followed by the conversion of sorbitol to fructose via sorbitol dehydrogenase. One of the best known mechanisms for generating fructose is the diabetic state, as hyperglycemia is well known to stimulate aldose reductase and induce the production of sorbitol and fructose [5].

However, there are other stimuli that activate the aldose reductase pathway. One of the most important ways is by eating fructose itself, possibly by the generation of uric acid that occurs during its metabolism [6]. Alternatively, hypoxia stimulates aldose reductase and endogenous fructose production, which has been shown in ischemic disease of the heart and kidney where the fructose has been shown to play a role in the injury [7,8]. Hyperosmolarity is another major stimulus for aldose reductase synthesis and activation, and fructose can be generated in the hypothalamus and kidneys in the setting of dehydration, where it has been shown to stimulate vasopressin release and induce kidney damage [9,10]. Recently, diets high in salt have been found to induce endogenous fructose production in the liver through its effect on raising portal vein osmolality stimulating the polyol pathway, with effects similar to that observed with dietary fructose intake [11]. The observation that hyperosmolarity is a stimulus for fructose generation is of concern in the patient with end-stage kidney disease in which hyperosmolarity is common.

Metabolism of fructose

In many respects, fructose appears very similar to glucose, and much of the metabolism of fructose and glucose is similar, especially following the first few steps in metabolism. However, fructose appears to be unique from glucose and most nutrients in its ability to induce obesity and diabetes. For certain, other components of the diet [such as *trans* fats, omega-6 fatty acids, and alcohol (especially beer)] may increase the risk for metabolic syndrome, but fructose appears to be especially capable of inducing features of metabolic syndrome. This appears to be due to its unique ability to reduce intracellular energy levels before it generates energy.

The intake of sugar (sucrose) results in its rapid breakdown in the gut by sucrase to generate the monosaccharides glucose and fructose. Fructose is then taken up by the specific glucose transporter 5 (Glut5) in the small intestine [12] where some of the fructose is metabolized [12]. However, as concentrations of fructose increase, the intestinal metabolism becomes saturated resulting in significant delivery of fructose to the liver via the Glut2, with the remaining 20%–30% of fructose being taken up by the kidney, adipose tissue, and other organs [13,14].

While fructose can be metabolized by hexokinase, most of the fructose is metabolized by fructokinase (ketohexokinase, KHK), which phosphorylates fructose to fructose 1-phosphate (Fig. 43.1). There are two isoforms of fructokinase, with fructokinase C (KHK-C), being the major isoform in the liver, and KHK-A isoform being more ubiquitously expressed. KHK-C is a rapid phosphorylator whereas KHK-A only slowly metabolizes fructose. Indeed, it is the KHK-C that appears to be the key enzyme driving the metabolic effects of fructose [15]. This is because the metabolism of fructose by KHK-C reduces the energy in the cell.

KHK-C is poorly regulated, and when it metabolizes fructose there is an immediate decrease in intracellular phosphate, adenosine triphosphate (ATP), and guanosine triphosphate (GTP) levels, leading to transient inhibition of protein synthesis and an accumulation of adenosine monophosphate (AMP) [16]. The decrease in intracellular phosphate stimulates activation of AMP deaminase, resulting in the generation to inosine monophosphate and eventually uric acid [17,18].

While uric acid is considered to be an antioxidant in the extracellular environment, when uric acid is produced intracellularly, it stimulates intracellular oxidative stress via activation of Nicotinamide adenine dinucleotide phosphate (NADPH) oxidase that is then translocated to the mitochondria, where it blocks mitochondrial ATP production by interfering with beta-fatty acid oxidation [19–21]. Fat synthesis is stimulated in association with endoplasmic reticulum stress, stimulation of transcription factors of sterol regulatory element-binding protein-a, and generation of citrate

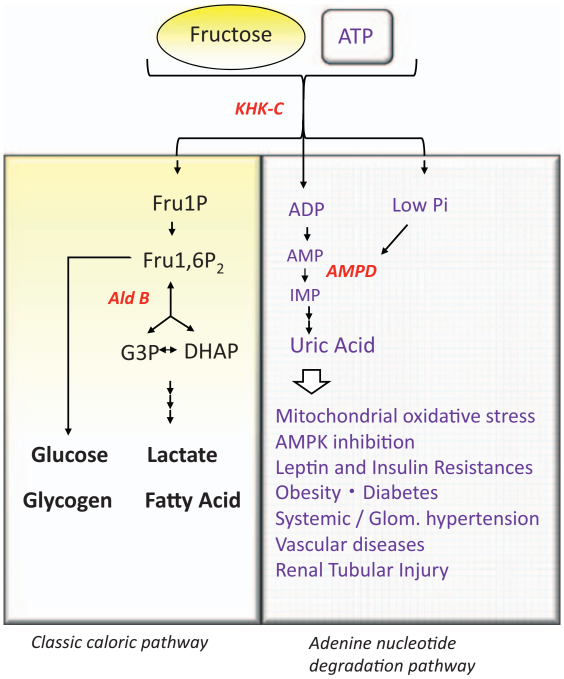

FIGURE 43.1 *Fructose metabolism:* In the classic "caloric" pathway, fructose is metabolized to fructose 1-phosphate followed by its metabolism by aldolase B and other enzymes, eventually generating the acyl glycerol, diacylglycerol, with the formation of glucose, lactate, glycogen, and triglycerides. The adenine nucleotide degradation pathway is associated with the stepwise reduction of ATP to uric acid. Most evidence suggest that this latter pathway is responsible for metabolic alterations, including mitochondrial oxidative stress, AMPK inhibition, leptin and insulin resistances, obesity, diabetes, systemic/glomerular hypertension, vascular diseases, and renal tubular injury with phenotypic changes. *AldB*, Aldolase B; *AMPD*, *AMP* deaminase; *AMPK*, AMP-activated protein kinase; *DHAP*, dihydroxyacetone phosphate; *Fru 1 P*, fructose 1-phosphate; *Fru1,6P*$_2$, fructose 1,6 bisphosphate; *G3P*; glyceraldehyde 3-phosphate; *KHK*, fructokinase; *low Pi*, low level of intracellular phosphate.

[21,22]. A stimulation of glycolysis also occurs, resulting in a persistence of the low energy state [23]. Consistent with activation of these pathways, the ingestion of fructose results in an acute increase in intracellular uric acid in the liver with release into the circulation. Intracellular uric acid increases, releasing uric acid into the circulation by 1 to 2 mg/dL that peaks 15 minutes to an hour after ingestion [24,25].

In contrast, when glucose is metabolized, the initial phosphorylation by glucokinase is tightly regulated such that intracellular levels of ATP do not fall, AMP accumulation does not occur, and activation of AMP deaminase is prevented.

Thus there are essentially two pathways of fructose metabolism by KHK-C. The first pathway is the classic "caloric" pathway in which fructose is metabolized to fructose 1-phosphate followed by its metabolism by aldolase B and other enzymes, eventually generating the acyl glycerol, diacylglycerol, with the formation of glucose, lactate, glycogen, and triglycerides. The second pathway is the adenine nucleotide degradation pathway associated with the stepwise reduction of ATP to uric acid (Fig. 43.1). Most evidence suggest that it is this latter pathway that is responsible for how fructose induces metabolic syndrome.

Fructose as a potential cause of hypertension, obesity, and metabolic syndrome

Experimental studies

Several investigators have demonstrated that rats on high-fructose diet, but not on glucose, developed features of metabolic syndrome, including hypertension, insulin resistance, and hypertriglyceridemia [26–29]. Mice also develop features of nonalcoholic fatty liver disease (NAFLD) and metabolic syndrome with fructose, although this occurs better if the fructose is provided in the drinking water [30]. This is likely due to the fact that liquid sugars result in both a greater load and faster absorption that results in higher concentrations of fructose in the liver, leading to more profound ATP depletion with greater activation of the adenine nucleotide degradation pathway [4]. The importance of the fructose pathway is further illustrated by the observation that mice fed a Western diet high in sugar and fat develop severe fatty liver and insulin resistance that is markedly less in mice lacking fructokinase [15].

Clinical studies

Fructose also drives obesity and metabolic syndrome in humans. In 2009 Stanhope et al. reported that the administration of fructose in beverages providing 25% of energy requirement for 10 weeks resulted in reduced insulin sensitivity, dyslipidemia, increased visceral adiposity, and enhanced hepatic lipogenesis that was significantly greater than that observed in control subjects given glucose [31]. A randomized controlled trial also demonstrated that only 2 weeks of fructose administration could induce many features of metabolic syndrome in men [32]. Subsequently, an interventional study by Lustig et al. found that isocaloric fructose restriction could improve features of metabolic syndrome in children [33]. Likewise, 8 weeks of provision of a diet low in free sugar content compared with usual diet significantly improved steatosis in the adolescent boys with NAFLDs [34].

Fructose as a mediator of kidney diseases

The possibility that fructose may play a role in the development of kidney disease is increasingly likely, given its potential role in driving hypertension and diabetes as well as well-known association between metabolic syndrome and CKD. Furthermore, there is some evidence demonstrating the role of fructose in tubulointerstitial fibrosis, glomerulosclerosis, and renal microvascular disease [35–38].

Experimental studies

The administration of fructose (60% diet) induced renal hypertrophy with tubular cell proliferation and low-grade tubulointerstitial injury, generating chemotactic factors such as monocyte chemoattractant protein-1 (MCP-1) by tubular cells and ICAM-1 in renal microvascular endothelial cells in rats [35–38]. Fructose also increased proteinuria with an acceleration of renal dysfunction and glomerulosclerosis in the remnant kidney model, suggesting that fructose initiated and accelerated the kidney injury. Importantly, these changes in the kidneys were not observed in rats fed an equivalent glucose-based diet [38]. The toxic effect of fructose in renal tubular cells is likely driven by uptake passage of fructose into the glomerular filtrate, uptake of urinary fructose via the fructose transporter, Glut5, into the proximal tubule, and metabolism by fructokinase in the cytosol [35]. Indeed, the metabolism of fructose in proximal tubular cells by fructokinase results in intracellular ATP depletion, oxidative stress, uric acid generation, and the production of chemotactic factors such as MCP-1 [36]. Finally, hemodynamic studies in rats documented that fructose intake alters renal autoregulation by inducing preglomerular arteriolar arteriosclerosis, resulting in glomerular hypertension and a reduction in renal blood flow [39].

Clinical studies

Several clinical studies indicated that fructose intake is positively associated with an elevation of serum creatinine, an induction of urinary albuminuria, and a decline in estimated glomerular filtration rate (eGFR) [40–42]. Specifically, the NHANES (1999–2004) found that intake of two or more sugar-containing beverages was associated with an increased risk of having albuminuria [41]. In prospective analysis using the Nurses' Health Study Cohort, a consumption of ≥2 servings per day of artificially sweetened (diet) soda was independently associated with eGFR decline ≥30% [odds ratio (OR) 2.02, 95% confidence interval (CI) 1.36–3.01] and ≥3 mL/min/1.73 m^2/year (OR 2.20, 95% CI 1.36–3.55) [42]. More recently, a study evaluating the association between all types of beverages and CKD risk in community-based cohort of black Americans also confirmed that both soda and sweetened fruit drinks are identified as a risk factor for incident CKD [43]. However, there remains some controversy. For example, one study reported that consumption of sugar-sweetened beverages was not associated with disease progression in CKD patients on the basis of either eGFR or albuminuria [44]. However, the negative data may relate to the level of exposure, as studies evaluating the effects of consumption of one soft drink or less usually do not see an association of soft drinks with kidney disease while those drinking two or more do find an association [42].

Fructose and uric acid

Fructose metabolism results in uric acid synthesis as a by-product

One of the mechanisms that potentiates the deleterious effect of fructose is uric acid. As mentioned previously, uric acid is generated in the process of fructose metabolism. Not only an acute rise of serum uric acid after fructose intake, but a chronic high-fructose ingestion also led to an elevation of uric acid levels. The intake of a large amount of fructose in men for 12 days markedly raised both serum and urinary uric acid levels [45].

Importantly, lowering uric acid by a xanthine oxidase inhibitor ameliorates most phenotypes of metabolic syndrome and kidney disease induced by fructose [26,46]. It also seems a case in humans as several pilot clinical trials have demonstrated that the treatment for hyperuricemia improves blood pressure and insulin sensitivity [22,37,46,47]. While uric acid was often considered an inert substance [32], or even a beneficial factor due to its antioxidative effects [48], accumulating evidence suggests that uric acid directly or indirectly acts on different cell types to be proliferative, proinflammatory, vasoconstrictive, and prooxidative [49–51].

Role of fructose-induced uric acid production in the development of metabolic syndrome, hypertension, and kidney disease

As discussed earlier, fructose metabolism by fructokinase is associated with adenine nucleotide turnover, with the stepwise degradation of AMP to its final end product, uric acid (Fig. 43.1). Indeed, the ingestion of fructose results in an acute increase in intracellular uric acid in the liver with release into the circulation. This has led to the development of a fructose tolerance test, which measures the change in serum uric acid following ingestion of a set amount of fructose [24]. While the original concern with fructose-induced hyperuricemia related to its potential risk to cause gout, there has been increasing evidence that the adenine nucleotide degradation pathway, and especially the uric acid generated, may be mediating many of the metabolic effects of fructose.

For example, several studies have reported that xanthine oxidase inhibitors, such as allopurinol and febuxostat, can block many of the features of fructose-induced metabolic syndrome, including the hypertriglyceridemia, insulin resistance, hypertension, and fatty liver [20,26,52,53]. Similarly, uricosurics also protect against fructose-induced metabolic syndrome in the rat [26]. One study in rats also showed that sucrose-induced type 2 diabetes was also associated with a loss of islet cell function that likely involved uric acid, as the islets were shown to express urate transporters and uric acid induced oxidative stress in pancreatic islet cells in culture [54].

High-fructose intake in humans is also associated with elevated serum uric acid, especially in the postprandial period [55]. In turn, hyperuricemia is also associated with hypertension, metabolic syndrome, and kidney disease [56]. While there continues to be debate on the role of uric acid in these conditions, there is increasing evidence that uric acid likely has a role in hypertension, insulin resistance, and CKD [56,57].

The potential mechanisms by which uric acid may be involved in driving metabolic disease have been intensively studied. Although it is an antioxidant in the extracellular environment, one of its earliest effects is to induce oxidative stress that involves both stimulation of the NADPH oxidase system and mitochondrial metabolism [21]. There is also a stimulation of NFκB in various cell types, including vascular smooth muscle cells and tubular cells, activating inflammatory pathways with the release of chemokines and vasoactive factors [51,58]. These include the stimulation of the intracellular renin−angiotensin system, endothelin, and thromboxane [59−61]. Renal tubular cells also develop oxidative stress and can undergo dedifferentiation into mesenchymal cells [58,62].

Renal handling of fructose in subjects with chronic kidney disease and dialysis

Fructose is absorbed in the gut primarily through the Glut5 transporter, and then is metabolized in the intestine, followed by the liver and then other sites. In subjects who have not been exposed to a lot of sugar, the expression the Glut5 transporter is low, and absorption of fructose is often poor, such that malabsorption is common. However, in subjects exposed to soft drinks or fructose-rich foods, the expression of Glut5 can be rapidly induced, resulting in increased absorption that can translate into stronger metabolic effects. Likewise, fructokinase is also induced by fructose, as well as its product, uric acid [20,54]. Thus a study in children reported that lean subjects showed significant fructose malabsorption to an oral fructose load, but it was less in those who were obese and minimal in subjects who had obesity and biopsy-proven NAFLD [63].

Subjects with CKD often have hyperuricemia associated with the reduction in kidney function [64−66] and might be expected to have upregulated Glut5 and fructokinase expression with more pronounced increases in serum fructose in response to an oral fructose challenge. However, while baseline serum uric acid levels are higher, the relative increase in uric acid was less in subjects with CKD [67]. In contrast, subjects on hemodialysis showed delayed absorption of fructose but with a greater rise in serum uric acid [68]. The reason for these findings is not fully understood. It is known that uric acid can inhibit xanthine oxidase in a negative feedback loop at least partially, so that the presence of high uric acid may have some effects to block its further production. It is also possible that subjects with CKD have a low ATP state that may result in less substrate availability for urate generation.

Guideline for fructose intake in chronic kidney disease patient

CKD patients are generally restricted in the intake of protein, phosphate, and salt, but often not for carbohydrate and sugars. Therefore CKD patients may be exposed to higher fructose intake and become vulnerable to metabolic effect of high fructose. Patients with CKD are at high risk for both heart disease and progression of their kidney disease. Many are also diabetic. However, once on dialysis, some subjects can become cachectic with a cachexia-like syndrome. Indeed, as debility increases, conditions such as obesity and hypertension may be associated with better survival, and a reversed pattern has also been observed for hyperuricemia. This has led to general questions on the ideal diet for the patient with kidney disease.

Our recommendation is that foods containing refined sugar and HFCS should be recognized as foods that may increase adipose mass, induce insulin resistance, and stimulate fatty liver. This is especially true for sugar provided in a liquid form, such as soft drinks, power drinks, sugary teas, and fruit punches. These drinks often contain a lot of fructose and the rapid intake can result in high-fructose concentrations in the liver that can increase its metabolic effects [4]. Fruit juices can also contain high concentrations of fructose and should be avoided [4]. In contrast,

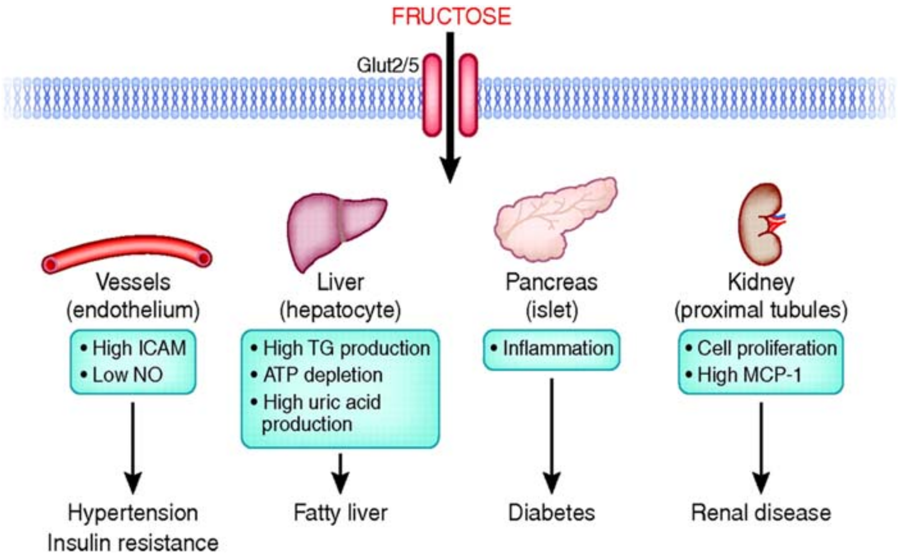

FIGURE 43.2 Effect of fructose in the development of hypertension, fatty liver, diabetes, and kidney disease. *Glut2/5*, Glucose transporter 2/5; *MCP-1*, monocyte chemoattractant protein-1; *TG*, Triglyceride. [74]. Source: *From Johnson RJ, Sanchez-Lozada LG, Nakagawa T. The effect of fructose on renal biology and disease. J Am Soc Nephrol 2010;21(12):2036–9.*

natural fruits contain less fructose and also have other components that either delay absorption (fiber) or block the metabolic effects of fructose (epicatechin, vitamin C) [69]. Indeed, we recommend natural fruit as the food of choice when an individual desires something sweet (taking into the potassium content of the fruit). Many fruits contain potassium, so this needs to be factored in the discussions when recommendations for fruit are given. In terms of recommendations related to refined sugar, we would follow the American Heart Association recommendation of limiting 25-g sugar (six teaspoons) for women and 37.5 g (nine teaspoons) for men as the daily limit [70].

In addition, special concerns include the following. First, for the subject with severe hypertension, reducing both sugar and salt is key. Both sugar and salt stimulate thirst and, hence, might lead to greater weight gain between dialysis runs. Fructose ingestion also leads to an immediate rise in blood pressure [71]. Further, there is evidence that sugar may drive some of the effects of salt [72]. Second, in the patient with comorbid liver disease, sugar is now recognized as the major risk factor for nonalcoholic fatty liver, and restriction of sugar is key to help prevent worsening of the liver disease [73]. Third, liquid sugar should be viewed as a risk factor for renal progression, and restriction of soft drinks is important in the subject with CKD, especially if it is progressing [74].

Of importance, however, is the subject with cachexia. We recommend liberalizing the diet fully for these individuals, as malnutrition may be a greater risk than obesity. Clinical judgment is important, but in the highly catabolic or wasted individual, the use of sugar to stimulate appetite and to increase weight mass may be beneficial.

Conclusion

There is increasing evidence that dietary exposure to fructose can possibly have substantial metabolic effects predisposing individuals to diabetes, hypertension, fatty liver, and kidney disease (Fig. 43.2), which is potentially mediated by an elevation of uric acid. Given the consideration of cardiovascular and metabolic comorbidities in CKD patients, fructose intake needs to be reduced unless the patients demonstrate evidence of malnutrition. More clinical studies are warranted to determine the effect of dietary fructose restriction on renal progression in CKD patients.

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PART VII

Special techniques for delivery of nutrients

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CHAPTER

44

Oral and enteral supplements in kidney disease and kidney failure

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Introduction

Protein-energy wasting (PEW) is used to describe the depletion of body protein mass, decreased fat mass, and/or energy fuel supplies in patients with chronic kidney disease (CKD) [1]. PEW is prevalent in patients with advanced CKD (Stages G3B-G5) [estimated glomerular filtration rate (eGFR) < 45 mL/min/1.73 m^2], with manifestations developing along with a reduction in the GFR and becoming more common as patients reach end-stage kidney disease (ESKD) requiring maintenance dialysis [2]. Depending on the method used to assess PEW, it is present in 20%–54% of people with advanced CKD [3–6] and up to 60% in maintenance dialysis patients [6–11]. Most patients exhibit mild-to-moderate degrees of PEW and 6%–8% have severe PEW [12,13].

The causes of PEW in advanced CKD are complex and multifactorial and include a buildup of uremic toxins that contributes to anorexia and reduced protein and energy intake, inflammation, and superimposed catabolism [14]. Diminishing appetite in Stage G4 with marked decreases in Stage G5 result in a spontaneous reduction in dietary energy and protein intake that is often accompanied by worsening nutritional status [15]. This is one of the most significant clinical indicators of progressive kidney disease. Moreover, the dialysis treatment itself is a catabolic process that contributes to PEW. The dialysis membrane, dialysis access, and nutrients lost during the dialysis procedure such as amino acids and protein reduce nutrient availability. These nutrient losses coupled with inadequate protein and energy intake contribute to the breakdown of muscle proteins and increases the risk of PEW. Metabolic derangements such as hyperparathyroidism, metabolic acidosis, endocrine disturbances, and decreased insulin also contribute to PEW. Lastly, increased production of inflammatory cytokines such as tumor necrosis factor-alpha and interleukin-6 also cause PEW (see Chapter 13: Causes and treatment of protein-energy wasting in kidney disease).

PEW is manifested by low levels of serum albumin or prealbumin, sarcopenia, weight loss, vascular calcification, and increased levels of C-reactive protein, and it is closely associated with increased risk of morbidity and mortality and impaired quality of life [2]. PEW is both preventable and treatable with an early diagnosis and nutrition interventions [i.e., nutrition counseling, oral nutritional supplements (ONS), and enteral nutrition (EN, tube feeding)].

The nutrition goals for treatment and management of CKD are dependent on the patient's nutritional status and metabolic condition, and the type and stage of kidney disease. Because of the high prevalence of PEW in patients with CKD, and its detrimental effects on quality of life, morbidity, and mortality, several nutrition guidelines and consensus statements have been developed to address prevention and treatment strategies for managing PEW [2,16–20]. In general, these documents provide recommendations for assessing, monitoring, and evaluating treatment for PEW and requirements for macro- and micronutrients and electrolytes. More recently, the 2020 Kidney Disease Outcomes Quality Initiative (KDOQI) Clinical Practice Guideline for Nutrition in CKD provided

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recommendations for medical nutrition therapy (MNT), which includes, but is not limited to, nutrition counseling and nutrition support [20].

ONS and EN (tube feeding) are the routes of choice for nutrition support in patients with, or at risk for, PEW [16,20,21]. However, the guidelines for the use of ONS and EN in CKD were developed based on expert opinion because: (1) large randomized controlled trials (RCTs) that assessed the effects of nutrition support on nutritional status and morbidity and mortality in patients with CKD are lacking and (2) there are a limited number of oral or enteral formulas that have been developed specifically to meet the metabolic needs of patients with CKD. Therefore their efficacies with regards to both nutritional benefits and prognostic effects in the CKD population have not been thoroughly examined. This chapter will address the oral and EN supplements used to prevent and treat established PEW in patients with advanced CKD [Stages G3B-G5 (nondialysis)] and ESKD [maintenance hemodialysis (MHD) and chronic peritoneal dialysis (CPD)]. In addition, the use of these ONS and EN in patients with nephrotic syndrome will be discussed briefly.

Advanced CKD [Stages G3B-G5 (nondialysis)]

Treatment of patients with ONS and EN

The nutritional challenge in treating patients with advanced CKD is to simultaneously ensure, on the one hand, the preservation of kidney function using low-protein diets and controlling blood pressure and blood glucose levels and, on the other hand, the prevention or treatment of established PEW. Part of the challenge is that these patients require close monitoring of protein and energy intakes and nutritional status before dialysis begins to detect and prevent PEW. This should be a priority since PEW in patients commencing dialysis is associated with higher morbidity and mortality rates during the first year of treatment [22]. Unfortunately, the majority of adults in the United States with CKD are unaware of their diagnosis; they never receive MNT and most remain poorly informed about how diet influences kidney disease management and progression. Most patients are not referred to or do not seek nutrition guidance from a nephrology registered dietitian nutritionist (RDN) (or international equivalent) for MNT until they develop kidney failure and start dialysis [23]. According to data from the US Renal Data System, less than 10% of CKD patients were referred to an RDN before the initiation of dialysis [24]. MNT has been demonstrated to improve clinical outcomes in CKD patients [25–27]. Until recently, clinical practice guidelines in kidney disease did not emphasize the role of RDNs in the treatment and management of patients with nondialysis-dependent CKD. However, the 2020 KDOQI Clinical Practice Guideline for Nutrition in CKD, which was developed in collaboration with the Academy of Nutrition and Dietetics, includes statements regarding MNT in patients with all stages of CKD, including posttransplantation [20].

A stepwise approach to nutrition intervention should be used to treat and manage patients with advanced CKD (see Fig. 44.1). Nutrition intervention begins with periodic nutrition assessments and nutrition counseling by an RDN in the form of MNT. The RDN should monitor nutritional status every 1–3 months and more frequently if there is inadequate nutrient intake, established PEW, or the presence of an illness that may worsen nutritional status, as these are predictive of increased morbidity and mortality risk [28]. Nutrition counseling, which is aimed at implementing behavioral change strategies that empower patients to adhere to the renal diet, is an integral component in the management of these patients. They require specialized nutrition care and ongoing monitoring by an experienced nephrology RDN to prevent nutritional inadequacies and subsequent PEW. When there is no improvement in markers of nutritional status (e.g., sufficient energy and protein intakes to meet nutritional requirements) or deteriorating nutritional status that places the patient at risk of PEW, more intensive strategies such as a 3-month trial of ONS is recommended [20]. The nutrition supplement should be specific for advanced CKD patients, that is, it should be energy dense with reduced protein and electrolytes (i.e., potassium, phosphate, and sodium) to meet the patient's high energy needs and conform to the low protein and electrolyte requirements. In patients with chronically inadequate intake and whose protein and energy needs cannot be met by nutrition counseling and ONS, a trial of EN (tube feeding) is suggested [20].

Although ONS and EN may be useful in advanced CKD patients with PEW, there have been very few studies that examined the effectiveness of these interventions on clinical outcomes these patients. Thus far, only one RCT [29] showed that a nonprotein calorie supplement was effective in preserving kidney function and nutritional status in advanced CKD patients on a low-protein diet. As a result, the evidence-based statements in the 2020 KDOQI guideline about ONS and EN in patients with CKD were developed based on expert opinion [20]. Finally, in patients with no obvious severe, superimposed catabolic illness, the presence of PEW in spite of aggressive nutritional management (e.g., ONS and EN) may be an indication to initiate dialysis treatment [30].

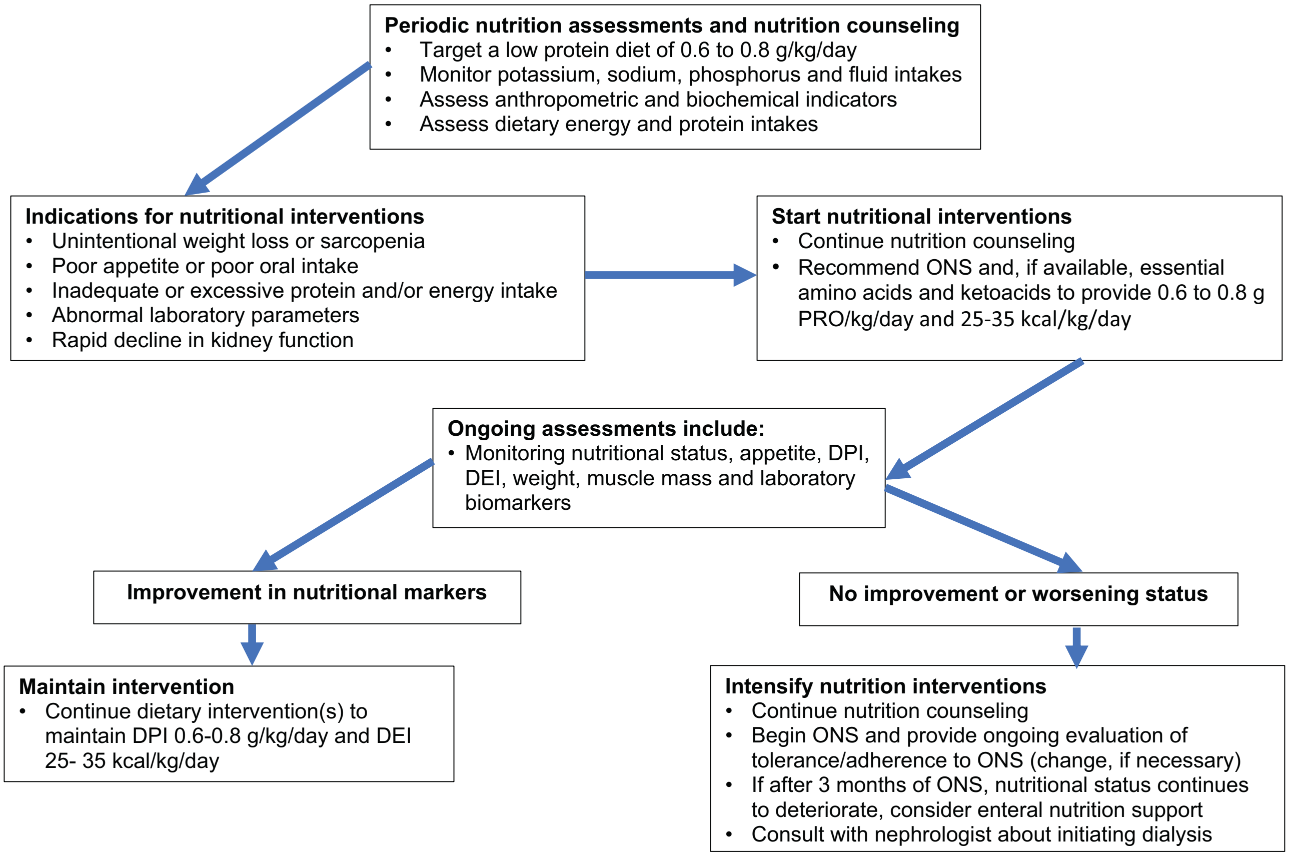
Periodic nutrition assessments and nutrition counseling
• Target a low protein diet of 0.6 to 0.8 g/kg/day
• Monitor potassium, sodium, phosphorus and fluid intakes
• Assess anthropometric and biochemical indicators
• Assess dietary energy and protein intakes
Indications for nutritional interventions
• Unintentional weight loss or sarcopenia
• Poor appetite or poor oral intake
• Inadequate or excessive protein and/or energy intake
• Abnormal laboratory parameters
• Rapid decline in kidney function
Start nutritional interventions
• Continue nutrition counseling
• Recommend ONS and, if available, essential amino acids and ketoacids to provide 0.6 to 0.8 g PRO/kg/day and 25-35 kcal/kg/day
Ongoing assessments include:
• Monitoring nutritional status, appetite, DPI, DEI, weight, muscle mass and laboratory biomarkers
Improvement in nutritional markers
No improvement or worsening status
Maintain intervention
• Continue dietary intervention(s) to maintain DPI 0.6-0.8 g/kg/day and DEI 25- 35 kcal/kg/day
Intensify nutrition interventions
• Continue nutrition counseling
• Begin ONS and provide ongoing evaluation of tolerance/adherence to ONS (change, if necessary)
• If after 3 months of ONS, nutritional status continues to deteriorate, consider enteral nutrition support
• Consult with nephrologist about initiating dialysis

FIGURE 44.1 Suggested algorithm for assessment of treatment of protein-energy wasting in patients with advanced CKD (stages 3–5). *CKD*, Chronic kidney disease; *DEI*, dietary energy intake; *DPI*, dietary protein intake; *EAA*, essential amino acids; *ONS*, oral nutritional supplements; *PRO*, protein. Source: *Modified from Kovesdy CP, Kopple JD, Kalantar-Zadeh K. Management of protein-energy wasting in non-dialysis-dependent chronic kidney disease: reconciling low protein intake with nutritional therapy. Am J Clin Nutr 2013;97:1163–77. Permission pending.*

Indications for ONS and EN

Essential amino acid and ketoacid preparations that are prescribed and administered with very low-protein diets for patients with advanced CKD are not addressed in this chapter (see Chapter 16: Dietary interventions to slow the progression of chronic kidney disease and improve metabolic control of uremia). Furthermore, recommendations for macro- and micronutrient intakes are discussed in detail in Chapter 29, Nutritional approaches and plant-dominant diets for conservative and preservative management of chronic kidney disease. An energy intake of at least 25–35 kcal/kg body weight (BW)/day and 0.6-0.8 g protein (PRO)/kg BW/day is recommended in patients with advanced CKD [20]. When spontaneous dietary intake cannot meet these requirements, ONS should be prescribed two to three times daily to ensure that the recommended intakes are met to prevent PEW or to treat the existing condition. Patients should be advised to take ONS preferably 1–2 hours after meals rather than as a meal replacement to maximize benefit [2].

Standard products for oral and EN support contain a mixture of whole protein and/or amino acids, glucose polymers, fat components and added vitamins, minerals, electrolytes, and trace elements. These products are not routinely recommended for patients with advanced CKD because they are usually high in protein and provide substantial amounts of electrolytes (i.e., phosphorus, sodium, and potassium) that may need to be limited in the diet. However, these products may be used by some patients because of cost and lack of availability of the specialized formulas on the global market. As such, regular monitoring and evaluation of serum chemistries are important, and implementations of the necessary changes to the ONS prescription are crucial measures to ensure the overall safety and effectiveness of oral nutrition supplementation.

Polymeric formulas developed specifically for patients with kidney disease are preferred since they contain modified amounts of protein and greater energy density (up to 2.0 kcal/mL), and they are electrolyte-restricted [31]. Some of the ONS are also nutrient-specific (i.e., composed solely of protein or nonprotein calories). A number of these products are well tolerated and have been shown to increase protein and energy intakes [32]. However, their effects on nutritional parameters, morbidity and survival, have not been examined fully in clinical trials. ONS are also available in different preparations (e.g., milkshake, juice, pudding, energy bar, or powder, which may be added to foods or beverages to increase protein and/or energy intake); the choice of preparation is dependent on the patient's preference, tolerance, and acceptability. Using a variety of preparations may decrease monotony, which can lead to flavor and taste fatigue and eventually nonadherence to the ONS [33]. The RDN should monitor and evaluate the patient regularly throughout the supplementation period, since adjustments to the ONS prescription may be necessary to improve adherence and to optimize effectiveness.

Table 44.1 provides a list of commercial supplements available in the United States and abroad for advanced CKD. Nepro LP (Abbott Nutrition Abbott Laboratories, Columbus, OH) (LP stands for Low Protein) and Suplena with Carb Steady (Abbott Nutrition Abbott Laboratories, Columbus, OH) are two examples of ONS for advanced CKD. These and other commercial products are designed for both oral nutrition and enteral feedings, and as supplemental or sole-source nutrition.

EN feedings are also indicated in advanced CKD patients who are hospitalized or institutionalized, and who are unable to consume adequate amounts of nutrients. Moreover, patients who cannot consume sufficient ONS to meet their needs, who have acute stress conditions, who have certain neurological diseases, dementia, pharyngeal, or esophageal obstruction, or who are unconscious, may require EN feedings [16,34]. EN is first administered through a nasogastric tube. When EN is expected to last more than 1 month, a perendoscopic or radiologic gastrostomy should be considered.

Chronic dialysis patients (Stage G5)

A detailed discussion of nutrition management of MHD and CPD is found in Chapter 31, Nutritional management of maintenance hemodialysis patients, and Chapter 32, Nutritional management of chronic peritoneal dialysis patients, respectively. Most of the clinical research that has addressed the pathophysiology, prevalence, and treatment of PEW in CKD has been performed in patients receiving MHD or CPD [16,21]. In these patients the reported incidence and prevalence of PEW varies from 25% to 70%, depending on the nutritional parameters that were assessed [6–11]. An increased mortality risk associated with PEW in dialysis patients has been described since the early 1980s [35–37]. Since then several RCTs and non-RCTs have examined the effects of ONS on improving nutritional status and clinical outcomes in patients receiving MHD [38–51] and CPD [47,52,53], although the studies in this latter group are limited. (See Table 44.2 for a list of RCTs and non-RCTs that examined the effects of ONS in patients undergoing MHD and CPD.)

Recommendations for dietary intake of macro- and micronutrients and electrolytes in patients receiving MHD and CPD are discussed in Chapter 31, Nutritional management of maintenance hemodialysis patients, and Chapter 32, Nutritional management of chronic peritoneal dialysis patients, respectively. The recommended intakes of dietary energy and protein for these patients are 25–35 kcal/kg BW/day and 1.2 g/kg BW/day,

TABLE 44.1 Nutrient content of specialized oral and enteral nutrition supplements for chronic kidney disease and kidney failure.

Manufacturer product	Serving size (mL)	Energy (kcal)	Protein (g)	Sodium (mg)	Potassium (mg)	Phosphorus (mg)	Fiber (g)
For nondialysis (low-protein products)							
Abbott Nepro LP	220	401	9.94	176	251	143	2.77
Abbott Suplena Carb Steady	237	420	10.6	190	250	170	6
Fresenius Kabi Fresubin Renal	200	400	6	136	200	110	2.4
Nutricia Renilon 7.5	125	249	9.1	85	30	8	0
For end-stage kidney disease (high-protein products)							
Abbott Nepro HP	220	401	17.82	154	233	158	2.77
Abbott Nepro Carb Steady	237	425	19.1	250	250	170	3
Nestle Novasource	237	475	17.4	210	192	154	NA
Victus Enterex Renal	237	472	20	275	255	113	4

NA, Not available.

TABLE 44.2 Randomized controlled trial (RCT) and nonrandomized controlled trial (NRCT) examining the effects of oral nutritional supplements (ONS) in patients undergoing hemodialysis (HD) and peritoneal dialysis (PD).

Authors (reference)	Dialysis modality	Study type	Study duration	Sample size	Nutritional entry criteria	Type of ONS	Nutritional and other relevant parameters significantly improved by ONS
Allman et al. [38]	HD	RCT	6 months	21	BMI < 27 kg/m^2	Energy supplement (glucose polymer commercial formula)	↑DEI; ↑body weight; ↑body fat; ↑lean body mass
Bolasco et al. [39]	HD	RCT	3 months	30	Serum albumin <3.5 g/dL, nPNA < 1.1 g/kg/day, and BMI > 20 kg/m^2	Protein supplement (AA commercial formula)	↑ePCR; ↑serum albumin; ↑total proteins; ↑body weight; ↑Hb; ↓CRP
Calegari et al. [40]	HD	RCT	3 months	18	SGA >9 and one other criteria: **1.** TST $< 90\%$ **2.** AC/AMC $< 90\%$ **3.** Serum albumin <3.5 g/dL **4.** BMI < 18.5 kg/m^2	Protein-energy supplement (food-based supplement)	↑SGA; ↑QoL
Cano et al. [41]	HD	RCT	12 months	186	Two out of four nutritional markers: **1.** BMI <20 kg/m^2 **2.** $>10\%$ weight loss within 6 months **3.** Serum albumin <35 g/dL **4.** Serum prealbumin <300 mg/L	Protein-energy supplement (commercial formula)	↑nPNA; ↑serum albumin; ↑serum prealbumin; ↑BMI
Cheu et al. [43]	HD	NRCT	13.5 months	470	Serum albumin <3.8 g/dL	Protein-energy supplement (commercial formula)	↑Serum albumin ↓Hospitalization
Fouque et al. [44]	HD	RCT	3 months	86	Serum albumin <40 g/L and BMI < 30 kg/m^2	Protein-energy supplement (renal-specific commercial formula)	↑DPI; ↑DEI; ↑SGA; ↑QoL
Hiroshige et al. [45]	HD	RCT (CO)	12 months	44	Serum albumin <3.5 g/dL and presence of anorexia	Protein supplement (BCAA commercial formula)	↑DPI; ↑DEI; ↑plasma albumin; ↑dry body weight; ↑body fat %; ↑lean body mass
Hung and Tarng [46]	HD	RCT	3 months	55	No criteria specified	Protein-energy supplement (renal-specific commercial formula)	↑DEI; ↑body fat mass
Scott et al. [48]	HD	NRCT	3 months	88	No criteria specified	Protein-energy supplement (renal-specific commercial formula)	↑Serum albumin; ↑QoL
Sezer et al. [49]	HD	NRCT	6 months	62	Serum albumin <4 g/dL, and/or $\geq 5\%$ loss of dry weight over the last 3 months	Protein-energy supplement (renal-specific commercial formula)	↑Serum albumin; ↑dry weight; ↑TST
Tomayko et al. [50]	HD	RCT	6 months	38	No criteria specified	Protein supplement (whey and soy commercial formulae)	↓IL-6 (whey and soy); ↑gait speed and walking distance (whey and soy)
Wilson et al. [51]	HD	RCT	9 months	46	↓ Serum albumin	Protein-energy supplement (commercial formula)	↑Serum albumin

(*Continued*)

TABLE 44.2 (Continued)

Authors (reference)	Dialysis modality	Study type	Study duration	Sample size	Nutritional entry criteria	Type of ONS	Nutritional and other relevant parameters significantly improved by ONS
Moretti et al. [47]	PD and HD	RCT (CO)	6 months	49	No criteria specified	Protein supplement (liquid hydrolyzed collagen commercial formula)	↑nPCR; ↑serum albumin
Gonzalez-Espinoza et al. [52]	PD	RCT	6 months	28	Moderate or severe malnutrition rated by SGA	Protein supplement (egg–albumin commercial formula)	↑DPI; ↑DEI; ↑nPNA; ↑serum albumin; ↑TST; ↑MAMA; ↑SGA
Teixido-Planas et al. [53]	PD	RCT	6 months	65	No criteria specified	Protein-energy supplement (commercial formula)	↑Body weight; ↑TST; ↑MAMC; ↑LBM; ↑creatinine LBM-related to body surface area; ↑creatinine generation rate; ↑lymphocytes

AA, Amino acid; *AC*, arm circumference; *AMC*, arm muscle circumference; *BCAA*, branched-chain amino acids; *BMI*, body mass index; *CO*, crossover; *CRP*, C-reactive protein; *DEI*, dietary energy intake; *DPI*, dietary protein intake; *ePCR*, equilibrated protein catabolic rate; *Hb*, hemoglobin; *IL-6*, interleukin-6; *LBM*, lean body mass; *MAMA*, midarm muscle area; *MAMC*, midarm muscle circumference; *nPCR*, normalized protein catabolic rate; *nPNA*, normalized protein nitrogen appearance; *QoL*, quality of life; *SGA*, subjective global assessment; *TST*, triceps skinfold thickness.

respectively [20]. Studies have shown that most MHD patients consume less energy and protein than recommended. In the HEMO Study, patients consumed an average of 23 kcal/kg/day and 0.93 g PRO/kg/day, which is less than recommended [54]. Several studies have evaluated dietary energy and protein intakes among patients receiving CPD and estimated a daily intake of 22–25 kcal/kg (from diet alone) and 0.85–1.1 g PRO/kg [55–59].

Peritoneal dialysis (PD) is associated with glucose absorption from the dialysate. Traditional PD solutions are high in glucose and provide about 300–600 kcal/day, depending on the peritoneal transport rate and the dialysis prescription [21,60]. These additional calories compensate for the potentially low energy intake in patients receiving CPD [61], but it may contribute to weight gain [62,63] and the metabolic syndrome [60] in some patients. Total energy intake is higher in patients receiving CPD than MHD because it includes calories absorbed from the dialysate; energy intake may be close to 30 kcal/kg/day in the former group. On the other hand, protein is especially important among patients receiving CPD because of the protein wasting that occurs during dialysis. It is estimated that 5–15 g of protein and 3–4 g of amino acids are lost per day in the dialysate effluent; these losses are substantially increased during episodes of peritonitis [21].

Treatment of patients with ONS and EN

Since MHD patients with PEW commonly ingest fewer calories than recommended, nutrition supplements prescribed to these patients should provide about 10 kcal/kg/day to attain the recommended intake. Providing nutrition support to dialysis patients in a timely manner, in the form of either ONS or EN, will ensure that they receive adequate protein and energy to meet their needs. ONS given two to three times a day can provide additional energy of 7-10 kcal/kg/day and protein of 0.3-0.4 g PRO/kg/day, depending on the formula used. These additional calories and protein make it possible to attain the recommended levels of protein and energy intakes that cannot be obtained spontaneously through a normal diet.

Few ONS specifically developed for dialysis patients are commercially available on the global market [1]. Table 44.1 provides a list of some commercial supplements available for patients receiving maintenance dialysis in the United States and abroad. Nepro HP (Abbott Nutrition Abbott Laboratories, Columbus, OH) (HP stands for High Protein) and Novasource (Nestle Health Science, Bridgewater Township, NJ) are two examples of ONS for chronic dialysis patients. These and other commercial products are designed for both oral and enteral feedings, and as supplemental or sole-source nutrition. Standard oral nutrition formulas are commonly used because specialized products may not be widely available in every country. If these standard products must be used, choose ones that are protein and energy dense, and limited in potassium, phosphorus, and sodium content. Moreover, they should not be consumed on a long-term basis.

The following practical rules may improve the efficiency of ONS [16,64]: (1) ONS should be given

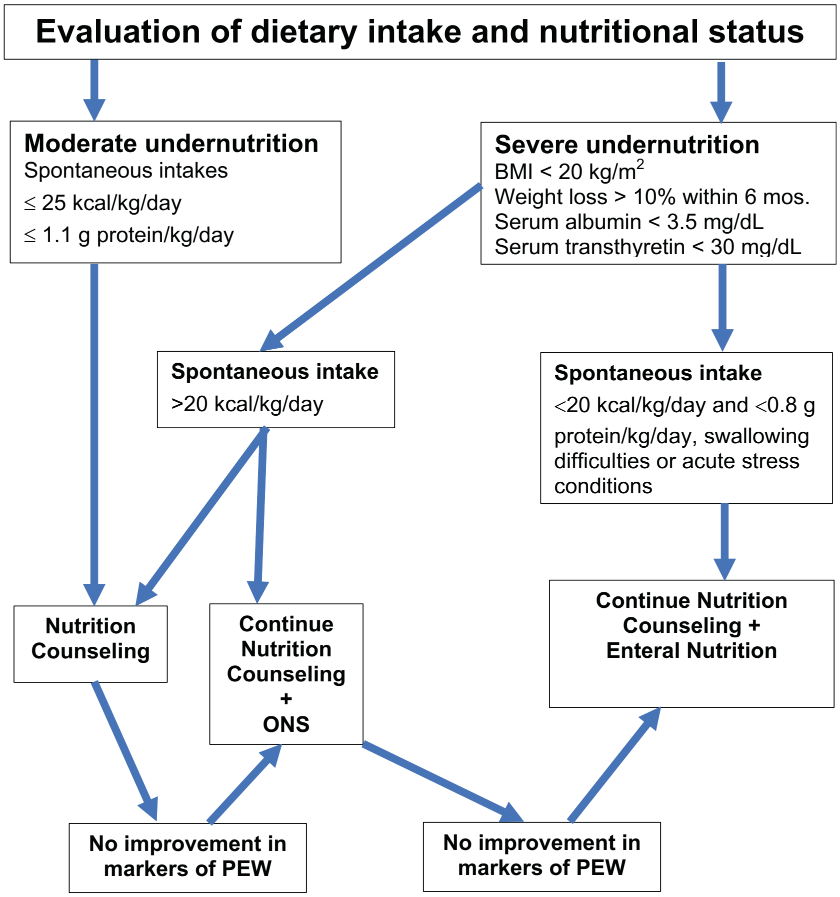
Evaluation of dietary intake and nutritional status
Moderate undernutrition
Spontaneous intakes
≤ 25 kcal/kg/day
≤ 1.1 g protein/kg/day
Severe undernutrition
BMI < 20 kg/m2
Weight loss > 10% within 6 mos.
Serum albumin < 3.5 mg/dL
Serum transthyretin < 30 mg/dL
Spontaneous intake
>20 kcal/kg/day
Spontaneous intake
<20 kcal/kg/day and <0.8 g protein/kg/day, swallowing difficulties or acute stress conditions
Nutrition Counseling
Continue Nutrition Counseling + ONS
Continue Nutrition Counseling + Enteral Nutrition
No improvement in markers of PEW
No improvement in markers of PEW

FIGURE 44.2 Algorithm for the management of PEW in maintenance dialysis patients. *BMI*, body mass index; *ONS*, oral nutritional supplements; *PEW*, protein-energy wasting. Source: *Modified from Cano NJ, Aparicio M, Brunori G, Carrero JJ, Cianciaruso B, Fiaccadori I, et al. ESPEN Guidelines on Parenteral Nutrition: adult renal failure. Clin Nutr 2009;28:401–14. Permission pending.*

separately from regular meals, usually 1–2 hours after the main meals to perform true nutrition supplementation and not simply a nutrition substitution; (2) ONS can be given during the hemodialysis treatment to prevent dialysis procedure-associated alterations of protein metabolism; and (3) a late evening meal or ONS may be useful to reduce the length of nocturnal nutrient deprivation and the associated increased consumption of endogenous protein and fat mass.

Table 44.2 summarizes the results of RCTs and non-RCTs of ONS administration versus no supplementation, nutrition counseling only, or treatment with intradialytic parenteral nutrition for MHD and CPD patients who had some evidence of PEW. Although these clinical trials were heterogeneous with regard to study design, the measured nutritional outcomes [e.g., serum albumin, subjective global assessment (SGA), dietary energy and protein intakes, body weight] improved in the 10 RCTs [38–41,44–47,50,51] and 3 non-RCTs [43,48,49] conducted in MHD patients, as well as the 3 RCTs performed in CPD patients [47,52,53].

EN (tube feeding) is indicated in chronic dialysis patients when PEW is associated with spontaneous protein and energy intakes less than 0.8 g PRO/kg/day and 20 kcal/kg/day, respectively, and when dietary intake does not improve sufficiently with nutrition counseling or ONS (see Fig. 44.2). In these patients, EN helps to maintain normal structure and functioning of the digestive tract [16]. A few cohort studies of EN in MHD patients have shown that nutritional parameters improved [65,66]; however, clinical trials of EN in adult CPD patients have not been published.

EN is most often used when patients are not able to tolerate oral feedings and ONS are not able to satisfy nutritional requirements in conditions such as severe anorexia, swallowing difficulties secondary to neurologic or head and neck diseases, the perioperative period, and superimposed systemic illnesses. In these situations, EN should provide all of the required macro- and micronutrients. Protein and hypercaloric nutritive mixtures are preferably used. When prescribing EN for patients with ESKD, the water, sodium, potassium, and phosphorus content of the preparation should be taken into account. If the duration of EN feeding is expected to exceed 1-month, surgical placement of a percutaneous endoscopic gastrostomy (PEG) or percutaneous endoscopic jejunostomy (PEJ) should be considered. Due to an increased risk of peritonitis, PEG or PEJ is contraindicated in adult CPD patients.

An algorithm for nutrition support of chronic dialysis patients with PEW has been proposed by the European Society of Clinical Nutrition and Metabolism (see Fig. 44.2) [67].

1. In patients presenting with mild nutritional depletion, as defined by insufficient spontaneous intakes, dietary counseling, and if necessary ONS, should be prescribed.
2. In patients exhibiting PEW and spontaneous dietary energy intake is >20 kcal/kg BW/day, dietary counseling and ONS should be prescribed. EN may be recommended when ONS cannot meet nutritional requirements.
3. In patients with PEW and spontaneous dietary energy intake is <20 kcal/kg BW/day, or in stress conditions, daily nutrition support is necessary. EN should be preferred to parenteral nutrition (see Chapter 45: Intradialytic parenteral nutrition, intraperitoneal nutrition, and nutritional hemodialysis).

Some patients receiving MHD do not respond to nutrition support. In these patients, therapeutic approaches, including treatments aiming to improve appetite, to decrease protein breakdown, and/or to promote protein synthesis, have been proposed in the EBPG [18]:

- Exercise training, which is demonstrated to improve protein synthesis and to increase muscle performance and possibly muscle mass, should be proposed after cardiovascular assessment establishes its safety.
- Similarly, in the case of severe PEW resistant to optimal nutritional intervention, a 3- to 6-month course of androgenic compounds may be given to MHD patients in the absence of contraindications. Such patients should be monitored at regular intervals for side effects (e.g., hirsutism, voice change, priapism, alteration in plasma lipids, liver tests, and blood tests for prostate cancer).
- Consider a 6- to 12-month trial of daily dialysis (either short daily or long nocturnal) as therapy for MHD patients who are frail, those who exhibit a failure to thrive and/or have PEW that is resistant to nutrition support and other therapies.

To improve protein nutrition, therapies such as the administration of essential or branched-chain amino acid supplements [39,45] and the modulation of inflammation by pentoxifylline, for example, have been proposed [68–71]. These data suggest that an integrated multimodal management that combines nutrition support, exercise and, in selected patients, anabolic and anticatabolic agents may be the optimal treatment for PEW in chronic dialysis patients [42].

Provision of ONS during the hemodialysis treatment

Over the last few years, an increasing number of dialysis facilities have encouraged and even provided patients with ONS to be consumed during the hemodialysis treatment. The International Society of Renal Nutrition and Metabolism has issued a statement regarding eating during hemodialysis, which states that “nutrition during dialysis should be considered as a part of the standard-of-care practice for hemodynamically stable patients who have no contraindications and no history of intolerance to consuming food during treatment” [72]. This practice is routine in many nations such as Germany, France, and the United Kingdom; it remains controversial in the United States and in some other countries. Several studies have indicated that provision of an ONS with a high protein and energy content during hemodialysis is associated with a modest improvement in serum albumin concentration and a slight increment in body mass index [73–75], SGA, and malnutrition–inflammation score [40,76]. In addition to improving these markers of nutritional status, providing ONS during treatment may also improve patient adherence and satisfaction [77]. More clinical trials are needed to establish whether this practice reduces morbidity and mortality.

Since many patients bring their own food and eat during the hemodialysis treatment, dialysis clinics could provide a specifically formulated ONS for dialysis patients at risk of or with established PEW. This would ensure that patients are receiving about 400 kcal and 20 g protein during each treatment. Dietitians could also use this time as an opportunity to provide nutrition education and to reinforce the importance of consuming adequate dietary energy and protein intakes to prevent and/or treat established PEW.

The other side of this debate is that providing ONS and meals during the dialysis treatment contributes to postprandial hypotension, reduction in treatment efficiency, gastrointestinal symptoms, aspiration, increased staff burden, and infection control and hygiene issues [72,78]. Controlled trials are needed to examine the safety and efficacy of providing meals and ONS during the hemodialysis treatment and its effects on outcomes.

Nephrotic syndrome

Nutritional and metabolic particularities of nephrotic syndrome

Patients with nephrotic syndrome exhibit specific metabolic disorders that should be taken into account when designing their nutritional management plan (see Chapter 28: Nutritional and nonnutritional management of the nephrotic syndrome). Insulin resistance is frequent and can be worsened by corticosteroid and other immunosuppressive treatments [79]. Metabolic studies showed similar rates of whole-body protein metabolism in patients with nephrotic syndrome as compared to controls. However, tissue-specific studies show that liver protein synthesis is increased whereas muscle protein synthesis is reduced [80]. Patients with nephrotic syndrome also exhibit abnormalities in lipid metabolism that mainly consist of increased plasma concentrations of low-density lipoprotein (LDL) cholesterol, lipoprotein (a), and very LDL [81]. These patients are also characterized by sodium retention [82], hypocalcemia, and low serum vitamin D levels due to the urinary losses of vitamin D and vitamin D transport protein [83].

Nutrition requirements, ONS, and EN

A personalized nutrition evaluation is needed for patients with nephrotic syndrome. High-protein diets, which had been proposed to prevent PEW, were shown to increase proteinuria and reduce kidney function [80,84]. On the other hand, modestly restricted low-protein diets have been shown to decrease proteinuria, to increase serum albumin levels, and to maintain nitrogen balance [84]. It should be emphasized that such regimens have only been investigated in clinically stable patients and during short-term studies (e.g., 1 month). Therefore the long-term effects of modestly reduced protein diets on nutritional status, as well as their tolerance by clinically unstable patients with nephrotic syndrome, are unknown [80,83,84].

The risk of PEW during long-term treatment with low-protein diets has not been evaluated in nephrotic patients. A protein supply of 1 g/kg BW/day or 0.8 g PRO/kg BW/day plus the compensation for urinary protein losses appears to be a good approach. Monitoring nephrotic patients by urinary urea excretion and urinary protein losses makes it possible to assess adherence to the prescribed regimen [84]. Other dietary recommendations include an energy intake of 30–35 kcal/kg BW/day, the exclusion of sugars that have rapid gastrointestinal absorption, and a limited fat intake [83]. Therapies that reduce proteinuria contribute to an improved serum lipid profile [81]. Regular exercise, vitamin D, and calcium supplementation have been proposed to prevent osteoporosis [83]. Because of water and sodium retention, sodium chloride intake should not exceed 4 g/day in adults [82].

The effects of ONS and EN have not been evaluated for the treatment of nephrotic patients with PEW. However, since these patients may need aggressive nutrition support, ONS as well as EN should be prescribed similar to patients with advanced CKD (i.e., with high-energy low-protein products).

Conclusion

The spectrum of kidney diseases includes very different nutritional and metabolic conditions that require specific nutrition management. Patients with CKD generally share a common phenotype with patients who have other chronic diseases that is responsible for similar losses of muscle mass, visceral proteins, and fat stores. The causes for PEW in these individuals include anorexia, reduced spontaneous nutrient intake, physical inactivity, anemia, inflammation, and insulin resistance. Although data concerning the treatment of PEW in patients with advanced CKD patients are limited, ONS or EN can be indicated when PEW or superimposed acute illnesses occur.

MHD and CPD contribute additional causes for PEW. The independent adverse effect of PEW on the survival of chronic dialysis patients has been known for nearly 40 years. In MHD patients, the beneficial effects of ONS on improving protein–energy nutritional status has been demonstrated; more clinical trials are needed to establish their effectiveness in CPD.

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C H A P T E R

45

Intradialytic parenteral nutrition, intraperitoneal nutrition, and nutritional hemodialysis

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Introduction

Protein-energy wasting (PEW) is a robust risk factor for unpropitious outcomes, including death, in maintenance hemodialysis (MHD) and chronic peritoneal dialysis (CPD) patients. Reduction in body mass index and muscle mass, low serum levels of albumin and transthyretin, inadequate appetite and food intake, and measures indicating inflammation are indicators of PEW. Adequately powered, randomized, double-blind clinical trials that examine whether nutritional support improves clinical outcome in MHD and CPD patients are not available. However, some randomized prospective clinical trials do give valuable insights and indicate that protein—energy status can be improved in MHD patients with PEW. Also, nonrandomized studies, some of which are retrospective, suggest that improving protein—energy status by nutritional intervention improves clinical outcomes in these patients. There is uniform consensus that dietary counseling and oral nutritional supplements should be the initial step in the management of patients with PEW. Low nutrient intakes and disease states, if present, that impair digestion and absorption of nutrients should be identified and treated. If patients are unable to eat adequate amounts of food or food supplements, enteral tube feeding which utilizes the patient's gastrointestinal tract for absorption of nutrients is the next most physiological method to provide nutrients. However, not uncommonly, patients are reluctant to accept an enteral tube as a method of feeding or, due to gastrointestinal disorders, they cannot receive sufficient nutrition by enteral tube feeding to satisfy their daily requirements. If these conditions persist, or are anticipated to persist, for more than several days, other techniques of nutritional support must be applied.

Intradialytic parenteral nutrition

Patients for whom enteral nutrition is medically contraindicated or who refuse or respond inadequately to enteral nutrition may be considered for intradialytic parenteral nutrition (IDPN). This treatment offers an alternative method for providing additional nutrients to MHD patients. When prescribed, IDPN is normally administered with each hemodialysis (HD). IDPN is generally infused into the venous line distal to the hemodialyzer at the beginning of the HD session and is usually continued until the end of the HD treatment. It should be emphasized that since most MHD patients undergo HD only three times weekly, IDPN must be viewed as only an adjuvant nutritional therapy, and it cannot be used as the sole source of nutritional support unless patients receive HD daily.

The components of commonly prescribed oral nutritional supplements are listed in Table 45.1, and the nutritional components of a typical IDPN solution are listed in Table 45.2. IDPN solutions are commonly prepared from base solution components. Base solutions for amino acids, carbohydrates, and lipids from which IDPN solutions are prepared can vary in concentrations: up to 10% of essential and nonessential amino acids, 50% or 70% D-glucose, and 10% or 20% lipid emulsions. The lipid infusions can be omitted for short

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TABLE 45.1 Content of selected nutrients in some currently available oral nutritional formulations.

	Total carbohydrates (g)	Total protein (g)	Total fat (g)	Total calories (kcal)	kcal/mL
Nepro (240 mL)	39.4	19.1	22.7	425	1.8
Nepro (1000 mL)	166.8	81	96	1800	1.8
Boost glucose control (237 mL)	20	14	12	250	1.06
Boost glucose control (1000 mL)	84	58.2	49.4	1060	1.06
Boost (240 mL)	41	10	4	240	1.0

These nutrients indicate the total amount present in the volume of the solution indicated in the first column. These nutritional supplements also contain other macroelectrolytes, trace elements, and multiple vitamins.

TABLE 45.2 Current recommended intradialytic parenteral nutrition (IDPN) formulations.

Dextrose (infusion rates)	Lipids (infusion rates)	Protein
Moderate-to-high dextrose: carbohydrate 4–6 mg D-glucose/kg/min	Lipids: 4 mg/kg/min or 12–12.5 g/h	Amino acids: 0.6–0.8 g/kg per hemodialysis treatment or per one IDPN bag
Noncarbohydrate controlled 6–8 mg D-glucose/kg/min		
Low dextrose: ≤3 mg/kg/min Low dextrose, no lipids: ≤3 mg/kg/min	Lipids: 4 mg/kg/min or 12–12.5 g/h no lipids	Amino acids: 0.6–0.8 g/kg per hemodialysis treatment or per one IDPN bag. Amino acids: 0.6–0.8 g/kg per hemodialysis treatment or per one IDPN bag

Dextrose and lipids are calculated based on variable infusion rates. Amino acids are calculated based on daily protein requirements or allowances for nonpregnant nonlactating, normal adults or nondialyzed patients with chronic kidney disease, which is 1.2–1.6 g/kg/day. This is not the daily requirement for a nondialyzed CKD patient. These solutions are designed to be infused in 3.5–4 h but some nephrologists may infuse over 3 h in MHD patients who have substantial renal function. Infusion of IDPN over 3 h will probably reduce efficiency of utilization of the nutrients and may increase the risk of complications (e.g., hyperglycemia, post-IDPN hypoglycemia). *CKD*, Chronic kidney disease; *MHD*, maintenance hemodialysis.

periods of time (e.g., up to about 2 weeks) or for longer periods of time if patients receive adequate amounts of the essential fatty acids by oral or enteral feeding. Additional components of IDPN solutions commonly include macro-electrolytes and often trace elements and multivitamin formulations. The mineral content of the amino acid, carbohydrate, and lipid solutions must be taken into consideration when prescribing additional minerals to be added to the IDPN solution. The composition of the final IDPN solution can be altered depending on the patient's nutritional needs and metabolic characteristics and the duration of the patient's HD session. Since manufacturing pharmacies often provide IDPN and total parenteral nutrition (TPN) solutions in bulk for many patients, modifying the nutrient composition of IDPN solutions may increase the cost of formulating the solutions.

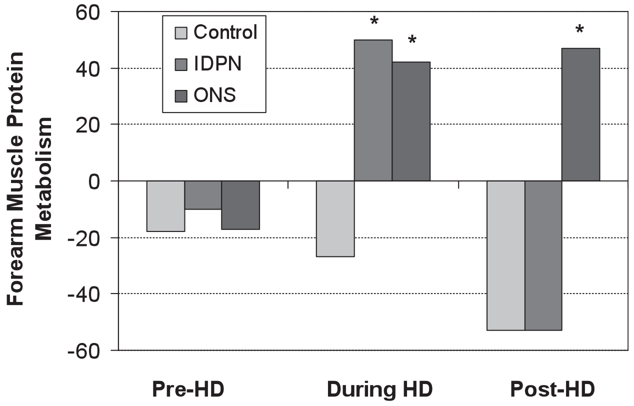

FIGURE 45.1 Effect of IDPN and oral nutritional supplements on forearm muscle homeostasis. *HD*, Hemodialysis; *IDPN*, intradialytic parenteral nutrition; *ONS*, oral nutritional supplements. Source: *Adapted from Pupim LB, Majchrzak KM, Flakoll PJ, Ikizler TA. Intradialytic oral nutrition improves protein homeostasis in chronic hemodialysis patients with deranged nutritional status. J Am Soc Nephrol 2006;17 (11):3149–57.*

Studies of the nutritional and metabolic effects of intradialytic parenteral nutrition

HD is often performed on patients who have been fasting for many hours. Pupim et al. (Fig. 45.1) investigated the acute effects of HD on protein turnover in MHD patients who were in the postabsorptive (fasting) state [1]. Eleven clinically stable MHD patients were fasted from at least 10 hours prior to the initiation of the study until 2 hours after the end of the HD. Total-body protein and forearm protein syntheses and

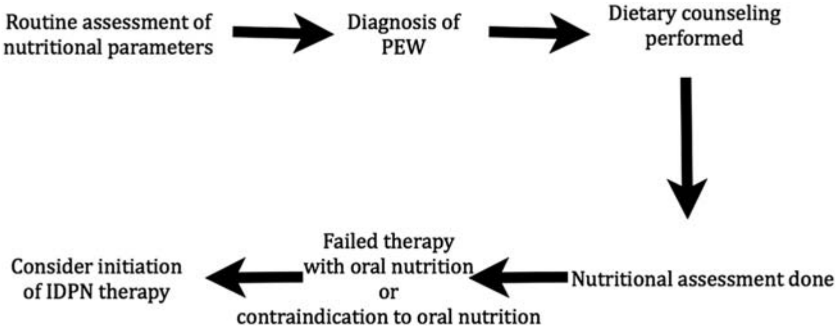
Routine assessment of nutritional parameters
Diagnosis of PEW
Dietary counseling performed
Nutritional assessment done
Failed therapy with oral nutrition or contraindication to oral nutrition
Consider initiation of IDPN therapy

FIGURE 45.2 Decision pathway in managing patients with protein-energy wasting.

degradation were measured immediately before, during, and 2 hours after the end of the HD session (Fig. 45.1). The patients received a constant infusion of L-(1$-^{13}$C) leucine and L-(ring-$^{2}H_5$) phenylalanine starting 2 hours before HD, which was continued until 2 hours after the HD. The results indicated that degradation of total-body protein and forearm muscle protein increased significantly during dialysis and remained increased at 2 hours after the HD. In comparison to baseline levels, during HD, there was an increase in protein synthesis that was observed in the forearm but not in the total body. Both total-body protein and forearm protein syntheses increased in the postdialysis period as compared with baseline levels. Net protein loss in the forearm increased significantly during dialysis but decreased to baseline levels after dialysis. During HD, total-body net protein balance became significantly more negative (Fig. 45.2).

There is reason to believe that IDPN may improve nutritional status of patients with PEW when it is due at least partly to inadequate protein or energy intake. First, data clearly indicate that the great preponderance of amino acids infused during IDPN are retained in the body and not removed by the hemodialyzer [2]. Also, in clinically stable MHD patients, there is at least a transient increase in protein anabolism during IDPN. In the previous study, Pupim et al. also examined seven clinically stable MHD patients who had no evidence of PEW while they received IDPN during a 4-hour HD [1]. Patients were fasted from 10 hours before a HD until 2 hours afterward, while they received the same amino acid isotope infusions as described earlier. Each IDPN treatment provided solutions containing 300 mL of 15% essential and nonessential amino acids, 150 mL of 50% glucose, and 150 mL of 20% lipids. When these fasting patients received IDPN, total-body protein and forearm protein syntheses were more positive and total-body protein degradation was lower as compared to when they did not receive IDPN (see earlier). During IDPN the patients also had significantly more positive net forearm protein balance and net total-body protein balance as compared to when they did not receive IDPN. The enhanced anabolic state observed with IDPN had abated at the end the 2-hour postdialysis period. These results indicate that nutritional support in the form of IDPN reduces body and forearm protein loss during HD in fasting, clinically stable MHD patients. Whether these anabolic effects of IDPN during HD would persist if the patients underwent many HD sessions with IDPN was not examined.

This same team of researchers subsequently compared intradialytic oral nutrition (IDON) to IDPN and also to no nutritional support in a separate study of eight clinically stable MHD patients [3]. The IDON provided 57 g of amino acids, 48 g of lipids, and 109 g of carbohydrates for a total of 1090 kcal. This solution was given in three equal feedings at 30, 90, and 150 minutes after the onset of the 4-hour HD. The IDPN solution contained 59 g of amino acids, 26 g of lipids, and 197 g of carbohydrates and 752 kcal. This IDPN solution was given starting 30 minutes after the initiation of HD and continued until the end of the HD session. Compared with when the patients received no nutritional intake, both IDPN and oral nutrition were associated with a significant increase in total-body protein synthesis and decrease in total-body protein degradation. Net total-body protein balance was significantly positive as compared with no nutritional support. At 2 hours after the completion of the HD session, total-body protein synthesis was still elevated only when the patients received IDON. Protein degradation did not differ significantly between the IDON and IDPN groups, but net total-body protein balance was significantly more negative with IDON as compared to IDPN or no nutritional treatment. In the 2 hours after dialysis, forearm protein balance was also significantly more positive when patients were given oral nutrition as compared to IDPN or no nutritional treatment. Although forearm protein degradation was similar among these three different treatments and during the 2-hour postdialysis session, the net forearm protein balance was significantly more positive with both IDON and IDPN during HD as compared to no nutritional support. Thus these short-term studies suggest that IDON may provide as safe and at least as effective a way as IDPN for enhancing anabolism in MHD patients.

Limitations of the clinical trials of intradialytic parenteral nutrition

Virtually all studies that have examined the effectiveness of IDPN are limited by one or more aspects of the experimental design, such as small sample size, and hence, inadequate statistical power, absence of a control group, poorly described inclusion criteria, or the fact that not all of patients receiving IDPN treatment met the criteria for a diagnosis of PEW. Commonly, studies did not describe the dose of dialysis received. The duration of the treatment and follow-up periods were often short. Many trials did not control the intake of food or oral nutritional supplements of the study patients. Occasionally, studies also offered defined amounts of food or oral nutritional supplements to the IDPN-treated or control patients. Due to these limitations, definitive conclusions regarding the effectiveness in IDPN in different patient populations cannot be drawn from the nonrandomized and the randomized studies. Some of the more seminal and influential of the nonrandomized IDPN studies, summarized in Table 40.3, and the randomized trials of IDPN, summarized in Table 40.4, will be reviewed.

Nonrandomized studies of intradialytic parenteral nutrition

The first report of IDPN in MHD patients was by Heidland and Kult [4]. They administered IDPN to 18 patients undergoing HD thrice-weekly over a 60-week period of study. During the last 90 minutes of each HD session, patients were given 16.7 g of essential amino acids, including histidine, and 250 mL of a mixture of D,L-malic acid, xylitol, and sorbitol. Some nonessential amino acids were added to the above mixture during the first 3 months. In 13 of the 18 patients, therapy was discontinued after 16 weeks. During each dialysis session, close to 100 g of protein in food was also prescribed. However, the intake of food was variable. Serum albumin and total protein levels were reported to increase significantly after 30 weeks of IDPN. Discontinuation of IDPN after 30 weeks resulted in significant fall in serum transferrin concentrations and a decrease in several complement proteins and hemoglobin levels.

Piriano and colleagues reported on 21 MHD patients who had lost at least 10% of their dry weight and were then treated with IDPN for 20 weeks [5]. Sixteen of these patients received IDPN that provided an average of 400 mL of 8.5% essential amino acids and nonessential amino acids with 400 mL of 50% glucose during each dialysis session. The other patients (5 out of 21 patients) were given a solution containing essential amino acids and 50% glucose. These five patients had lost at least 15% of their dry weight. The volume of IDPN provided in these five patients was not provided and the dialysis dose and the comorbid conditions are not clear. In both of these groups, there was no increase in serum albumin levels, and neither group experienced weight gain. However, the patients who did not have hyperparathyroidism and who received the essential and nonessential amino acids did display an increase in body weight.

In 47 MHD patients with severe PEW who received IDPN for 3 months, Bilbrey et al. reported that survivors had a significant increase in serum albumin levels [from 3.30 ± 0.38 (SD) to 3.71 ± 0.30 g/dL, $P < .001$] and transferrin levels (165 ± 37−200 ± 62 mg/dL, $P < .001$) [16]. In the nonsurvivors, there was no increase in serum albumin or serum transferrin levels. Duration of IDPN therapy, dialysis dose, and comorbid conditions was not reported.

In a retrospective study, Capelli et al. compared the survival of 50 patients who received IDPN to 31 patients who did not [6]. All 81 patients in the study had low serum albumin levels. At the beginning of the study, oral nutritional supplements and/or nutritional counseling were given for 2 months to all 81 patients in the study. The 31 patients who improved during oral nutritional supplements/nutrition counseling, and therefore did not receive IDPN, served as controls. The patients who did not respond to this nutritional treatment were then given IDPN. The patients treated with IDPN had a body weight that was 10% less than their desirable weight and/or had at least a 10% weight loss. In the control group, low body weights or a history of recent weight loss were not consistently present. The IDPN provided, per dialysis session, a 10%- or 20%-lipid emulsion (200−500 kcal), 50 g of essential amino acids, and a variable amount of D-glucose based on the diabetic status of the patient. Mortality was 48% in controls versus 36% in the IDPN-treated patients ($P > .05$), and time to death in the nonsurvivors was significantly greater in the IDPN-treated patients: 16.9 ± 7.9 (SD) versus 7.5 ± 4.2 months ($P < .01$).

Foulks et al. reported the results of a nonrandomized study of 72 patients with PEW who failed to respond to dietary counseling and who received IDPN [20]. Responders were classified as those who manifested at least a 10% increase in dry body weight or an increase in serum albumin of ≥ 0.5 g/dL while they received IDPN. Mortality was significantly lower in the patients who responded to IDPN. The serum albumin before IDPN was inaugurated was significantly lower in the responders as compared to the nonresponders [2.2 ± 0.7 (SD) versus 3.0 ± 0.8 g/dL ($P < .0001$)]. The body weights were similar in the responders and nonresponders both before and after treatment with IDPN. During the 6 months prior to initiation of IDPN, responders had higher hospitalization rates ($P < .0001$). However, during IDPN therapy, only 52% of responders were hospitalized as compared with 76% of nonresponders ($P < .0001$). The hospitalization rate decreased significantly only in the responders. It is possible that the improved clinical course of the responders was due to the IDPN and the patients' enhanced nutritional status. However, it is also possible that increased morbidity of the nonresponders impaired their ability to respond to the IDPN with a rise in serum albumin of ≥ 0.5 g/dL and also led to greater hospitalizations and mortality.

The largest study of IDPN retrospectively compared 1679 MHD patients who received IDPN to 22,517 matched control MHD patients who did not receive IDPN [7]. The IDPN prescriptions were not uniform in the 1679 patients. After adjustment for case mix and predialysis serum creatinine levels, those patients who had baseline serum albumin concentrations ≤3.3 g/dL and were treated with IDPN, as compared to those who had similar serum albumin levels but who did not receive IDPN, displayed a significant reduction in the odds ratio for death at 1 year. The IDPN-treated patients who had serum albumin levels ≥3.5 g/dL showed a significant increase in 1-year mortality. This is suggestive that IDPN may be less beneficial in patients with less severe PEW or inflammation. The survival effect of IDPN was greater in those MHD patients who had predialysis serum creatinine levels of 8.0 mg/dL or lower.

In another nonrandomized study, Hiroshige et al. reported results of IDPN therapy in 10 MHD patients who had PEW and were greater than 70 years of age [8]. Eighteen other MHD patients with PEW who refused IDPN were treated with dietary counseling and served as controls. The IDPN-treated group received this therapy for 1 year. The IDPN solutions that they received contained 200 mL of 50% glucose, 200 mL of a 20% lipid emulsion, and 200 mL of 7.1% essential amino acids per dialysis session. There were no major differences in baseline nutritional measures between the two groups. There was a significant increase in serum albumin and transferrin, body weight, triceps skinfold thickness, and midarm muscle circumference in the IDPN-treated group. All of the patients in the control group showed a significant decrease in each of these parameters. The control group also displayed a decrease in plasma essential amino acid concentrations during the course of the study. In the IDPN-treated group, plasma levels of essential amino acids and some nonessential amino acids increased and 3-methylhistidine levels fell. There were no deaths in the IDPN-treated group as compared to five deaths in the control group ($P < .02$).

Randomized prospective controlled trials of intradialytic parenteral nutrition

Randomized controlled studies of IDPN are summarized in Table 45.3. A total of 26 MHD patients with PEW were studied by Cano et al. for 12 weeks [9]. A total of 12 patients were randomized to receive IDPN, and 14 patients with a similar degree of PEW did not receive IDPN. The patients receiving IDPN demonstrated a significant increase in body weight, serum albumin and transthyretin (prealbumin) levels, midarm muscle circumference, skin test reactivity, plasma leucine concentrations, and apolipoprotein A-1 levels. The control patients did not manifest an increase in any of these measures. For many of these markers the IDPN group had statistically nonsignificant lower baseline values that could have predisposed to the increase in these values during IDPN. The IDPN solution provided 1.6-g lipid/kg body weight and 0.08 g of nitrogen from essential and nonessential amino acids/kg body weight. Although in the IDPN group plasma apolipoprotein A-1 levels increased, plasma lipid levels did not change. The authors concluded that the high-fat content of the IDPN solutions is effective and safe.

Guarnieri et al. studied 18 MHD patients, most but not all of whom had PEW [10]. Patients were randomly assigned to one of three IDPN treatment regimens according to the amino acid content of the solutions. Patients received either (1) only essential amino acids, (2) a combination of essential and nonessential amino acids, or (3) no amino acids with an isocaloric infusion of 5% glucose. Minerals, vitamins, and trace elements were given with each of the three IDPN treatments. These infusions were given thrice-weekly for 2 months. There was a significant increase in body weight ($P < .05$) only in the patients who received essential amino acids alone. This was the only change in any of the three groups.

In a subsequent study, 21 MHD patients were randomly assigned to receive IDPN for 6 months with essential amino acids (11 patients) or with a mixture of essential and nonessential amino acids (10 patients) as their only nitrogen source [10]. The mean serum

TABLE 45.3 Selected nonrandomized trials of intradialytic parenteral nutrition (IDPN).

Study, first author, year published	Design	Treatment duration	No. w/PEW	Parameters measured	Outcome
Heidland, 1975 [4]	18 pts; 16.75-g EAA, 100 kcal; no control	60 weeks	Most did not	Alb, total protein, complement levels, transferrin	Increase in serum Alb, total protein, transferrin, complement levels after 16 weeks therapy in 13 pts. When therapy was discontinued for 6 weeks, decrease in serum complement and transferrin
Piriano, 1981 [5]	16 pts: 16.5-g EAA + 1 NEAA, 200-g glucose 5 pts: 10.2-g glucose/EAA only	20 weeks	5 (in EAA group lost >15% of usual BW)	BW	In EAA + NEAA group, 8 pts gained >10% BW, other 8 lost weight. Pts in EAA group gained weight if did not have acute illness
Powers, 1989 [16]	18 pts; 250 mL 50% glucose, 250 mL RenAmin	46–165 infusions	All	Weight gain, Alb, TSF, MAMC	Weight gain (12.6 ± 4.9 lb) in 11 of 18 pts. No change in serum Alb
Bilbrey, 1989 [17]	20 pts; 50-g EAA + NEAA, 50-g lipid, 125-g glucose	90 days minimum	All	BW, MAMC	Only MAMC improved
Matthys, 1991 [18]	10 pts; 16.75-g EAA	3 months	All	Quality of life, Hct, BW, degree of edema	BW increased starting from the first month of therapy ($P < .01$). Scoring index of general condition increased ($P < .01$)
Bilbrey, 1993 [19]	47 pts; 400 mL 15% AA, 150 mL 70% glucose, 250 mL 20% lipids	90 days minimum	All	Alb, transferrin, mortality	29 survived, 18 died. Survivors had increase in Alb, transferrin. No data on cause of death, dialysis dose
Chertow, 1994 [7]	1679 pts: 1.2 g protein/kg, 15 kcal/kg 22,517 pts: no IDPN	12 months or until death		Alb, URR, odds of death	Decrease in mortality in IDPN-treated pts who had serum Alb ≤3.3 g/dL
Capelli, 1994 [6]	50 pts: 50-g EAA, 50-g lipid, 125-g glucose, dietary supplemented (discontinued once IDPN started) 31 pts: dietary supplements	9 months	All had Alb <3.5 g/dL, BW < 90% of desirable BW or BW loss >10% over 2 months	Alb, BW, mortality	32 of 50 treated pts and 16 of 31 untreated pts survived. Weight gain in treated survivors, no weight gain in survivors who were untreated. No weight gain in nonsurvivors in either group. 6 months of IDPN before change in weight or serum Alb
Foulks, 1994 [20]	72 pts; 0.64 g N/kg, 3.78 kcal/kg as lipids, glucose	Mean of 159 days in responders, 222 days in nonresponders		Mortality, hosp. rate	Decreased mortality and hospitalization rate in responders
Smolle, 1995 [21]	16 pts; 0.8-g/kg EAA + NEAA	16 weeks		Alb, skin test reactivity, WBC, SCr	NA
Cranford, 1998 [22]	43 pts; 63 g EAA + NEAA, 18.4-g lipid, 92.5 g carbohydrates	6 months		Alb, BUN, hospitalizations	NA
Hiroshige, 1998 [8]	10 pts: 200 mL 50% glucose, 200 mL 7% EAA, 200 mL 20% lipids 18 pts: dietary counseling	12 months	All	BW, BMI, TSF, MAMC, Alb, transferrin, plasma AA profile, mortality	All IDPN-treated pts survived, 5 pts without IDPN therapy died (3 due to sepsis, one due to GI bleeding) during study period
Mortelmans, 1999 [23]	26 pts (16 pts completed study, 10 pts withdrew); 250 mL 50% glucose, 250 mL 20% lipids, 250 mL 7% AA	9 months	All	BW, MAMC, lean body mass, transferrin, serum pre-Alb levels	BW increased ($P < .05$); serum transferrin, transthyretin increased. TSF increased ($P < .05$). No such change in pts who withdrew
Blondin, 1999 [24]	45 pts	6 months	All had mean Alb <3.2 g/dL ± 0.4	Alb, BUN, morbidity, URR, hosp. rate	Decrease in hosp rate ($P < .05$), increase in serum Alb ($P < .05$)
Cherry, 2002 [25]	24 pts; 250 or 500 mL 10% AA, 250 mL 50% glucose, 250 mL 20% fat emulsion	4.3 months (mean)	All	Alb, dry BW	Increase in dry BW, serum Alb
Dezfuli, 2009 [26]	196 pts. IDPN no control group	3–12 months	All	Serum albumin	72% of patients had increase in serum Alb. with a mean increase of 0.4 g/dL

Alb, Albumin; *BMI*, body mass index; *BUN*, blood, urea, nitrogen; *EAA*, essential amino acids; *HD*, hemodialysis; *IDPN*, intradialytic parenteral nutrition; *IV*, intravenous; *MAMC*, midarm muscle circumference; *NA*, not available; *NEAA*, nonessential amino acids; *PEW*, protein-energy wasting; *PNA*, protein equivalent of total nitrogen appearance; *TSF*, triceps skinfold; *URR*, urea reduction ratio.

albumin level was normal at baseline, and the average baseline energy intake prior to IDPN initiation was low. The mean baseline body weight and protein intake were marginally decreased. During IDPN with the essential and nonessential amino acids, but not with the essential amino acids alone, there was a significant decrease in serum albumin levels and an increase in normalized protein nitrogen appearance (nPNA).

The largest prospective randomized study was the French Interdialytic Nutrition Evaluation Study (FineS) [11]. A total of 186 patients, aged 18–80 years, undergoing MHD for more than 6 months were randomly assigned to receive IDPN ($n = 93$) or to not receive IDPN ($n = 93$). IDPN was given during dialysis sessions for 1 year. Both the IDPN-treated group and the control group received oral nutritional supplementation as part of the study design. Patients included in the study had at least 2 of the following indicators of PEW: (1) edema free weight loss of greater than 10% over the previous 6 months, (2) serum albumin <3.5 g/dL, (3) body mass index <20 kg/m^2, and (4) serum transthyretin <30 mg/dL. The exclusion criteria were (1) single-pool Kt/V <1.2, (2) TPN received within the 3 months preceding the study, (3) severe comorbid conditions that adversely affect 1-year survival, (4) less than 12 hours of dialysis treatment per week, (5) fasting serum triglyceride levels >300 mg/dL, and (6) hospitalization at the time of randomization. The nutritional intake, including energy intake, from all sources was monitored at baseline and at 3, 6, 12, 18, and 24 months after the onset of IDPN. The follow-up period was up to 2 years.

At months 3, 6, and 12, IDPN provided with each HD session, respectively, the equivalent of 6.6 ± 2.6 (SD), 6.4 ± 2.1, and 6.1 ± 2.2 kcal/kg and 0.26 ± 0.08, 0.25 ± 0.09, and 0.24 ± 0.10 g/kg of amino acids. To estimate the time-averaged daily dose, these estimates should be multiplied by 3 (three hemodialyses per week) and divided by 7 (the number of days in the week). At months 3, 6, and 12, oral supplements provided 5.9 ± 2.6, 5.8 ± 2.5, and 5.6 ± 2.7 kcal/kg/day and 0.39 ± 0.18, 0.38 ± 0.18, and 0.37 ± 0.18 g protein/kg/day. There was patient-to-patient variability as well as variability among HD centers with regard to the intake of nutrients from the IDPN and from spontaneous eating.

The results indicated no statistical difference in mortality, hospitalization rates, and indicators of PEW between the patients assigned to IDPN and the control patients. Both treatment groups showed no change from baseline in Karnofsky scores, nor was there any difference between the two groups in the change in these scores from baseline. The authors noted that although this was the largest prospective randomized trial to date, it was still underpowered. Since both groups received oral nutritional supplements, it is not unlikely that the failure to demonstrate any differences in outcome between the IDPN and control groups may have been due to the substantial intake of oral nutritional supplements that both groups received. Those patients in both treatment arms who had an increase in serum transthyretin to greater than 30 mg/L within the first 3 months of the trial displayed an approximately 50% decrease in mortality at 2 years.

The most recent multicenter randomized trial was conducted by the German IDPN-Trial group [12]. A total of 107 MHD with PEW were studied to assess the impact of IDPN on prealbumin and other measures biochemical and clinical measures of nutrition. Patients who were randomized to the intervention group received IDPN three times per week for 16 weeks followed by a treatment-free period of 12 weeks and nutrition counseling. The main inclusion criteria included moderate-to-severe PEW (Subjective Global Assessment score B or C), MHD for more than 6 months, the presence of two out of the following three criteria: serum albumin <35 g/L, serum prealbumin <250 mg/L, and phase angle alpha <4.5 as determined by bioelectrical impedance analysis). Nutrition counseling was started at the time of randomization. The standardized control group (nonintervention group) received nutrition counseling only. The key outcome measure was the effect of IDPN on serum prealbumin levels. A total of 83 patients were studied in the final analysis out of which 39 patients were in the IDPN group and 44 patients were in the control group.

This trial demonstrated significantly improved prealbumin levels at 16 weeks of IDPN treatment [mean change in serum prealbumin: +26.31 ± 58.66 (SD) mg/L in the IDPN group; −1.84 ± 49.35 mg/L in the controls; IDPN vs controls, $P = .02$]. This response was sustained during a treatment free follow-up period of 12 weeks. An ≥15% increase in serum prealbumin was observed at 4 weeks in 41% of the 39 patients in the IDPN group versus 20.5% of the 44 patients in the control group. No data were provided to justify the greater than or equal to 15% increase in serum prealbumin from baseline as a threshold for a responder to IDPN, and this value did not seem to be prespecified in the protocol. The mean improvement in serum prealbumin (+26.31 mg/L) levels in the IDPN group did not reach the threshold of >30 mg/L that was shown to be associated with reduction in mortality in the FineS study. There was also a trend toward more patients who received IDPN, as compared to controls, who attained a significant increment in serum prealbumin concentrations of

≥ 30 mg/L at week 16 (48% in the IDPN treatment group vs 31.8% in the control group, $P = .1164$). Serum albumin levels in the IDPN group did not improve significantly, and the authors of the study believed this was due to the short duration of IDPN treatment and because the sample size was not powered enough to detect a difference. A post hoc analysis showed an inverse correlation between serum C-reactive protein (an indicator of inflammation) and albumin levels that could account for the unexpected decrease in serum albumin in some patients.

Advantages and disadvantages of intradialytic parenteral nutrition

Advantages to IDPN include the nutritional support that it provides to patients with each dialysis session independent of their appetite, anorexia, or gastrointestinal function. Since the nutrition is given intravenously, the compliance of the patients or the willingness or the ability of the patient to cooperate does not materially affect this aspect of their nutritional intake. There is no need for an additional vascular access, because IDPN is given through the patient's preexisting access. The nutrient composition and the quantity of IDPN can be controlled and modified as needed. The excess fluid administered with intravenous infusions can be removed as it is infused during HD and should not add to the water load of the patient.

Disadvantages to IDPN therapy as it is usually given are that the nutritional supplements can only be given for about 9–12 hours weekly because it is given only during HD. Therefore IDPN, since it is generally provided three times weekly, cannot be the sole source for adequate nutrition. Since IDPN is given intravenously, it presents a nonphysiological circumvention of the normal gut–nutrient interactions. Hence, it does not contribute to the direct trophic effects of oral or enteral nutrition on the gastrointestinal tract. There is rapid clearance of nutrients from the blood with IDPN—much faster than is found with oral or enteral feeding into the stomach. Usually, IDPN adds significantly to the costs of dialysis therapy.

Adverse effects of intradialytic parenteral nutrition

Adverse events that have been reported include nausea, hyperglycemia, muscle pain, and post-IDPN reactive hypoglycemia. However, the published data on adverse effects of IDPN are limited; about 12%–14% of patients in two randomized controlled trials experienced such events [11,12]. It is difficult to analyze the clinical significance of adverse effects from IDPN in these published studies because the duration of treatment was short and the follow-up was limited.

Indications for intradialytic parenteral nutrition

In patients who are able to eat, there is a consensus that adequate nourishment should be provided using the oral route with normal food with or without food supplements. Tube feeding should be considered for patients who are unable to maintain adequate protein–energy status solely by eating. Tube feeding is more physiologic than intravenous feeding and can have valuable trophic effects on the gastrointestinal tract. Tube feeding is also safe and inexpensive. For MHD patients who cannot be adequately nourished by oral intake and tube feeding or when these routes of nourishment are not safe for a patient, IDPN should be considered. IDPN cannot be used as the sole source of nutrition for patients who undergo MHD only thrice-weekly. There are some MHD patients whose nutritional needs cannot be met by either oral intake or tube feeding combined with IDPN, and they may require TPN. Definitive indications for IDPN are difficult to identify, because benefits regarding morbidity and mortality have not been shown conclusively in randomized, prospective trials of IDPN. There are no randomized prospective clinical trials of IDPN that have the combination of adequate sample sizes, sufficiently long duration of study, appropriate key outcome measures, and an experimental protocol with the necessary rigorous design (Table 45.4). It is important to note that despite the fact that there are no adequately powered prospective randomized clinical trials, the data that are available so far support the thesis that enteral feeding or IDPN benefit survival in MHD patients with PEW [13].

Considerations for intradialytic parenteral nutrition prescription by health-care workers in the United States

In the United States the approval for the initiation of IDPN for an MHD patient is based on the insurance coverage of the particular patient, although the coverage criteria are likely to change. Patients with Medicare insurance may have their IDPN covered by the Part D program of Medicare if they are outpatients. For hospitalized patients, IDPN is covered under Medicare Part A. The criteria that Medicare currently uses to approve initiation of IDPN coverage are

TABLE 45.4 Randomized prospective trials of intradialytic parenteral nutrition (IDPN).

Study, first author, year published	Design	Treatment duration	Number with PEW	Parameters measured	Outcome
Wolfson, 1982 [2]	8 pts. EAA + NEAA + glucose solution versus normal saline	NA	NA	Amino acid losses into dialysate with and without IDPN	There was a small increase in amino acid losses into dialysate during IDPN
Toigo, 1989 [27]	11 pts: 26.5-g modified EAA 10 pts: 24-g EAA + NEAA	6 months	None	Nerve conduction velocity, Alb	Decrease in serum albumin in EAA + NEAA group
Cano, 1990 [9]	12 pts: 0.08-g N/kg (per HD session) from EAA + NEAA, 1.6 g/kg (per HD session) lipids 14 pts: no intervention	3 months	All	BW, appetite, MAMC	Increase in calorie (9 kcal/kg/d) and protein intake (0.25 g/kg/d) in IDPN-treated pts
McCann, 1999 [28]	19 pts; 70% glucose, 15% amino acids, 20% lipids	11 weeks	NA	Delivered Kt/V, URR	Reduction in delivered Kt/V in pts who received amino acid-containing IDPN
Navarro, 2000 [29]	17 pts	3 months	NA	NA	Positive net balance of amino acids. Increase in PNA, serum Albumin transferrin
Cano, 2006 [30]	17 pts: olive oil—based IV lipid emulsion 18 pts: soybean oil—based IV lipid emulsion	5 weeks	NA	NA	Both groups showed similar improvement in nutritional status, plasma lipid, oxidative and inflammatory parameters
Cano, 2007 [11]	IDPN: 89 pts Control: 93 pts	12 months	All	Primary endpoint, all-cause mortality; secondary endpoints, hosp. rate, BW, Karnofsky score, BMI	No difference in hospitalization rate or mortality between two groups
Thabet, 2017 [31]	20 pts. IDPN + IV vitamins compared to 20 pts received IV vitamins alone	6 months	All Baseline serum albumin was 3.02 and BMI was 19		
Marsen, 2017 [12]	39 pts:IDPN + standard nutrition counseling 44 pts received standard nutrition counseling alone	16 weeks	All	Prealbumin, transferrin Subjective global Assessment (SGA) Score SF-12 Health-related short-term quality of life survey	IDPN given three times a week resulted in increase in greater or equal to 15% increase in serum prealbumin over baseline at week 4 in 41% of the 39 patients

Note: Only clinical trials with eight or more patients are listed. *Alb*, Albumin; *BMI*, body mass index; *EAA*, essential amino acids; *HD*, hemodialysis, *PEW*, protein-energy wasting; *IDPN*, intradialytic parenteral nutrition; *IV*, intravenous; *MAMC*, midarm muscle circumference; *NA*, not available; *NEAA*, nonessential amino acids; *PNA*, protein equivalent of total nitrogen appearance; *URR*, urea reduction ratio.

summarized in Box 45.1. The coverage of IDPN by Medicaid (insurance coverage by the state for qualified individuals) is not uniform. Many state Medicaid programs in the United States do cover IDPN. The private insurance carriers loosely follow Medicare criteria for approval of IDPN, but coverage for IDPN is uneven and some costs may be transferred to the patient. Most Health Maintenance Organizations do not provide coverage for IDPN. Medicare, Medicaid, and most commercial private insurance carriers recommend that IDPN is to be discontinued if serum albumin is >3.8 g/dL for more than 3 consecutive months.

Nutritional hemodialysis and intraperitoneal nutrition

Nutritional hemodialysis

Adding essential and nonessential amino acids to hemodialysate will result in an uptake of amino

BOX 45.1

United States Medicare Part D criteria for approval to initiate IDPN (intervention for malnutrition: patient qualification criteria)

1. Patient given intensive dietary counseling, emphasizing the need for increased protein and/or calorie intake, for a minimum of 1 month with no evidence of clinical improvement (i.e., rise in serum albumin and/or weight)
2. Initiation of oral supplementation attempted with no improvement in and/or weight gain after 1–2 months
3. Evidence of continued protein malnutrition as documented by:
   - **A.** A 3-month average serum albumin <3.5 g/dL
   - **B.** Progressive decline in serum albumin over 3 months to <3.5 g/dL
   - **C.** nPNA (nPCR) <0.8 g protein/kg/day or documentation of inadequate protein intake

   or

   Evidence of continued calorie malnutrition as documented by:
   - **A.** Current weight <90% of ideal body weight
   - **B.** BMI < 18 or
   - **C.** Weight loss greater than 5% over three months.
4. Recommendation by physician for prescribing IDPN therapy

acids into blood, which can be substantial [12]. When 139 g of an amino acid mixture is added to the total dialysate concentrate used during a typical 4-hour HD session, there is a net transfer of 39 g of amino acids from dialysate into the patient during the routine HD [12]. When 46 g of a mixture of 20 essential and nonessential amino acids are added to the dialysate concentrate, the plasma amino acid concentrations remain similar to those in the plasma of fasting patients suggesting that there is little or no net transfer of amino acids to or from the patient. The increase in osmolality in the hemodialysate is not a substantial limiting factor when adding glucose with amino acids to hemodialysate, since even adding glucose monohydrate to create a dialysate glucose concentration of 500 mg/dL will only add about 28 mosm/L to dialysate osmolality.

Although it is possible to provide the patient's daily need for essential and nonessential amino acids in the hemodialysate, it is not feasible to provide all of the patient's energy requirement through the hemodialysate. The total energy intake from the hemodialysate will be grossly inadequate for the patient's daily needs. Of course, the needed glucose and lipids can be either ingested or infused intravenously during HD. At the least, providing amino acids during HD should eradicate the catabolic effects of amino acid losses during HD that patients will sustain when they fast during this procedure [3]. Theoretically, adding amino acids to hemodialysate should be a less expensive treatment than IDPN for providing adequate amino acid nutrition during HD, because the amino acids do not have to be sterilized in solution. Lowering the hemodialysate flow rate has been done by some investigators to increase the fractional extraction of amino acids and glucose from the dialysate into blood [14]. The advantage of this approach is the increased efficiency and, hence, reduced cost of the quantities of amino acids taken up from the dialysate, but the disadvantage is the decreased efficiency of dialysis.

Intraperitoneal nutrition

The addition of amino acids to peritoneal dialysate appears to increase protein synthesis during peritoneal dialysis and raise serum or plasma concentrations of several proteins and amino acids [15]. By substituting amino acids for some of the glucose in peritoneal dialysate, this treatment also allows for a reduction in the dialysate glucose concentrations, which is often of metabolic benefit to the patient, with little or no loss of the osmotic pressure. Generally, a mixture of essential and nonessential amino acids is added to a typical peritoneal dialysate solution that may be further modified to reduce the glucose concentration. The final composition of the dialysate will generally contain a concentration of 1.1% amino acids. This solution is used for one or two of the peritoneal dialysate exchanges each day. To ensure uptake of about 80% of the amino acid content, a dwell time of 4–6 hours is recommended.

Again, to prevent excessive osmolality of the dialysate solutions, the energy that can be provided from these solutions is not substantial. When patients receive intraperitoneal nutrition, they should be encouraged to consume a nutrient intake or undertake tube feeding that provides at least most of their needs for energy and most other nutrients. However, care must be taken to prevent an excessive load of amino acids and protein from the combined intakes of intraperitoneal and oral or enteral nutrition. High serum urea levels, metabolic acidosis, and even some uremic symptoms can develop from such intakes.

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CHAPTER

46

Nutritional management of patients treated with continuous renal replacement therapy

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Introduction

Acute kidney injury (AKI), a common complication in the intensive care unit (ICU) associated with high mortality rate [1], more often occurs in the context of multiple organ failure syndrome than as an isolated condition [2]. As a consequence, metabolic and nutritional requirements of patients with AKI in the ICU are affected not only by the acute uremic state, but also by the underlying comorbidities and associated complications. Approximately 4%–6% of all critically ill patients with AKI will require some form of renal replacement therapy (RRT) during their ICU stay [3,4]. Currently, continuous RRT (CRRT), along with prolonged intermittent RRTs (PIRRTs) such as sustained low-efficiency dialysis (SLED), represents the primary choice in critically ill patients; in fact, these RRT modalities allow for a better hemodynamic stability with efficient fluid removal and metabolic control [5]. By lowering the dialysis or replacement-fluid flow and extending the duration of treatment to often more than 24 hours, rates of solute clearance, osmolality shift, and ultrafiltration rate are significantly reduced, resulting in better hemodynamic tolerability and clinical stability. Because of the efficiency of CRRT, nutritional losses can be very important, thus requiring a close coordination between nutritional support and CRRT itself [2,6,7].

In this chapter, nutritional implications of CRRT will be reviewed, with emphasis on nutrient balance, and the recommendations on nutritional support in patients with AKI in the ICU requiring CRRT will be discussed.

Continuous renal replacement therapy overview

CRRT is widely considered one of the preferred RRTs modalities for critically ill patients with renal dysfunction (AKI or critically ill patients with previous end-stage renal disease (ESRD) on maintenance hemodialysis), especially in cases complicated by hemodynamic instability and/or acute brain injury. Running in a continuous manner even for more than 24 hours, CRRT allows slower fluid and solute removal, thus obtaining a better hemodynamic tolerance and reducing the risk of rapid osmolality shifts. Veno-venous modalities of CRRT are currently the standard of care. Several modalities of CRRT are available (Table 46.1), each primarily depending on the mechanism used for solute transport, diffusion, and convection (Fig. 46.1), which can be used separately or combined. In the case of diffusion, dialysis fluid routinely runs counter-current to the blood flow inside the filter, creating a concentration gradient that will allow for solutes to diffuse through the hemofilter membrane. In this case, solute removal is mainly dependent on molecular weight, with smaller molecules being removed more easily than larger molecules. Continuous veno-venous hemodialysis (CVVHD) is the continuous modality that exclusively applies diffusion. Convection generates a much higher volume removal (ultrafiltrate) across the hemofilter by applying a high transmembrane pressure gradient, which drags predetermined fluid volume and solutes with it. In this case, both small- and medium-size solutes are effectively removed. Because of high fluid removal (solute clearance is proportional to volume removed), replacement fluids are needed to restore volume and

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TABLE 46.1 Continuous renal replacement therapy modalities.

RRT type	Clearance modality	Replacement fluid	Dialysate	Duration (h)
CVVH	Convection	X		24
CVVHD	Diffusion		X	24
CVVHDF	Convection and diffusion	X	X	24
SLED	Diffusion		X	6–12
SCUF	Convection			6–12

CVVH, Continuous veno-venous hemofiltration; *CVVHD*, continuous veno-venous hemodialysis; *CVVHDF*, continuous veno-venous hemodiafiltration; *RRT*, renal replacement therapy; *SLED*, sustained low-efficiency dialysis; *SCUF*, slow continuous ultrafiltration.

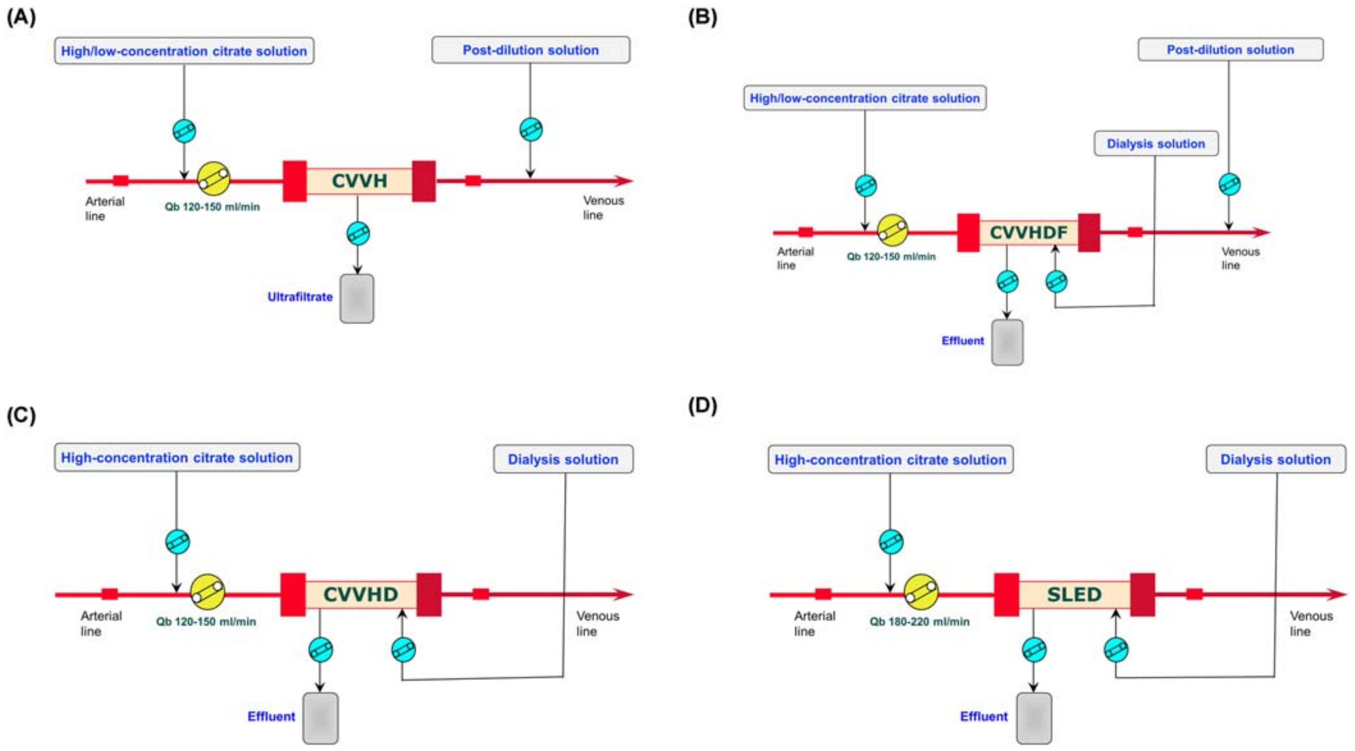
(A)
High/low-concentration citrate solution
Post-dilution solution
CVVH
Arterial line
Qb 120-150 ml/min
Venous line
Ultrafiltrate
(B)
Post-dilution solution
High/low-concentration citrate solution
Dialysis solution
CVVHDF
Arterial line
Qb 120-150 ml/min
Venous line
Effluent
(C)
High-concentration citrate solution
Dialysis solution
CVVHD
Arterial line
Qb 120-150 ml/min
Venous line
Effluent
(D)
High-concentration citrate solution
Dialysis solution
SLED
Arterial line
Qb 180-220 ml/min
Venous line
Effluent

FIGURE 46.1 The main modalities of RRT for AKI in the ICU: (A) CVVH, (B) CVVHDF, (C) CVVHD, and (D) SLED. *AKI*, Acute kidney injury; *CVVH*, continuous veno-venous hemofiltration; *CVVHD*, continuous veno-venous hemodialysis; *CVVHDF*, continuous veno-venous hemodiafiltration; *ICU*, intensive care unit; *RRT*, renal replacement therapy; *SLED*, sustained low-efficiency dialysis.

electrolytes. Continuous veno-venous hemofiltration (CVVH) is the modality that relies only on convection. The contemporary adoption of both solute removal techniques is a characteristic of continuous veno-venous hemodiafiltration (CVVHDF), a RRT modality that requires the use of both dialysis and replacement fluids. Dialysis and replacement fluids contain electrolytes and buffers at different concentrations. In CVVH the adoption of prefilter replacement fluid dilutes the actual plasma concentration entering the hemofilter, thus reducing the effective clearance, but in parallel may prolong filter life reducing the risk of clotting [8]. With conventional intensity CVVH, the differences in small solute clearance with pre- or postfilter replacements are negligible [9]. Independently from the dialysis modality, the most recent international guidelines on AKI recommends prescribing an effluent volume of at least 25 mL/kg/h, to achieve an effectively administered dialysis dose of 20 mL/kg/h, taking into account all treatment interruptions and downtime (i.e., temporary and unscheduled suspension of CRRT administration) [10]. Clinical trials have not demonstrated any advantage correlated with higher RRT doses (more than 35–40 mL/kg/h), emphasizing on the contrary the possible clinical disadvantages related to deficiency of vitamins, micro- and macronutrients lost in the effluent, as well as the risk for inadequate antibiotics levels [11,12]. In this regard, because most nutritional substrates are small and have a sieving coefficient, defined as the ratio of ultrafiltrate to plasma solute concentration, that approximates 1, their clearance is affected mainly by effluent rate, which makes the difference in nutrient losses between various modes of CRRT negligible. Other modalities of RRT, commonly denominated PIRRT or SLED, are characterized by 8- to 12-hour sessions and share most advantages of both the conventional intermittent RRT and CRRT [13]. PIRRTs, predominately based on diffusive mechanism for solute transport, have been shown to be safe and convenient, providing an excellent control of electrolytes and fluid balance [14]. Usually, the modality of CRRT selected usually depends on institution preference, local experience and logistics, fluid status, and metabolic/electrolyte abnormalities.

Continuous renal replacement therapy's components and their implications for nutritional support

When discussing the nutritional effects of CRRT, it is important to understand how CRRT evolved. Considering recent advancements in CRRT technology in the last decade [15], the factors that have a recognized impact on nutrition are replacement and dialysis fluids, and the choice of the anticoagulation modality.

Replacement and dialysate fluids

Replacement fluids are used to restore electrolytes and volume when CRRT modalities that exclusively or in part are based on convection are applied (CVVH and CVVHDF). In predominantly diffusion modalities (CVVHD and CVVHDF), dialysis fluids are used to establish a concentration gradient across the filter membrane.

A variety of commercially solutions are available, with different electrolytes and buffer compositions (Table 46.2). The selection of replacement or dialysate fluid is crucial to optimize the CRRT prescription and it usually depends on patients' metabolic, electrolyte, and acid–base profile. The different buffers utilized in CRRT fluids include bicarbonate or bicarbonate yielding substrates such as acetate, lactate, and citrate. Some of the dialysate and replacement fluids commonly used in the dialysis/hemofiltration procedures may provide energy substrates in the form of acetate, lactate, citrate, and glucose (Table 46.3). Lactate provides 0.33 kcal/mmol (3.7 kcal/g), and because only 6% of the infused lactate will be eliminated during CRRT, the amount of extra energy provided can be important. Assuming a buffer solution containing 40 mmol/L of lactate running at 2 L/h, this alone may account for as much as 500 kcal/day. Currently, bicarbonate-based solutions are preferred over lactate-based solutions, due to better control of acidosis, reduced lactate accumulation, and better hemodynamic tolerance [16,17]. Replacement and dialysis solutions also contain a variable amount of dextrose, usually ranging from 0 to 110 mg/dL. This may impact the amount of energy gain, if high dextrose concentration replacement/dialysate fluids are used, or net energy loss if glucose-free solutions are used instead; thus it should be taken into account when prescribing nutrition therapy.

Anticoagulation

During CRRT and PIRRT, an anticoagulation strategy is required to avoid RRT interruption and blood losses/transfusion need due to coagulated filter and/or extracorporeal circulation. Currently, continuous infusion of unfractionated heparin still remains the most adopted anticoagulation strategy for the extracorporeal circulation of RRT, despite the increased bleeding risk associated with this therapeutic approach. Several alternative strategies have been tested focusing at providing the anticoagulation of the extracorporeal circuit only, that is, aiming at the *regional anticoagulation* of the extracorporeal circulation without interfering with the systemic patient's hemostasis. Above all the possible anticoagulation methods, the suggestion from the most recent Guidelines on AKI, supported by several randomized trials designed to compare different strategies [18–24], is to use regional citrate anticoagulation (RCA) for all patients with and without an increased bleeding risk who do not have contraindications for citrate [10]. During RCA, citrate is infused into the inflow limb of the extracorporeal circuit at rates proportional to blood flow, providing the anticoagulation of the hemofilter and circuit lines by chelating ionized calcium in the blood, thereby blocking the clotting cascade at multiple steps. The citrate infusion rate is modulated to reach a concentration in the hemofilter around 2.5–3 mmol/L, which corresponds to ionized calcium levels in the extracorporeal circuit of 0.3–0.4 mmol/L. Because calcium–citrate complexes are characterized by high diffusive/convective clearance, with a significant amount of calcium being lost in the effluent fluid, an infusion of calcium (as chloride or gluconate) is generally required, to maintain the systemic ionized calcium levels within the normal range. The amount of citrate and calcium–citrate complex returning to the patient represents the metabolic load of citrate and corresponds to the difference between the citrate infused and the amount lost in the effluent.

TABLE 46.2 Electrolyte compositions of the most commonly adopted commercially available continuous renal replacement therapy solutions.

Solutions (mmol/L)	Prismasol 2 (Baxter)	Prismasol 4 (Baxter)	Hemosol B0 (Baxter)	PrismOCal B22 (Baxter)	Phoxilium (Baxter)	Biphozyl (Baxter)	multiBic 2 (Fresenius)	multiBic 4 (Fresenius)	Ci-Ca Dialysate K2 Plus (Fresenius)	Ci-Ca Dialysate K4 Plus (Fresenius)	multi Plus Dialysate (Fresenius)
Sodium	140	140	140	140	140	140	140	140	133	133	140
Potassium	2	4	0	4	4	4	2	4	2	4	2
Magnesium	0.5	0.5	0.5	0.75	0.60	0.75	0.5	0.5	1	1	0.75
Chloride	111.5	113.5	109.5	122	115.9	122	111	113	115.75	117.75	109.7
Calcium	1.75	1.75	1.75	0	1.25	0	1.5	1.5	0	0	1.5
Phosphate	0	0	0	0	1.2	1	0	0	1.25	1.25	1
Bicarbonate	32	32	32	22	30	22	35	35	20	20	35
Lactate	3	3	3	0	0	0	0	0	0	0	0
Glucose	6.1	6.1	0	0	0	0	5.55	5.55	5.55	5.55	5.55

TABLE 46.3 Calorie equivalent of carbohydrate metabolism substrates in dialysis/hemofiltration fluids.

Substrate	Source	Molecular weight	kcal/mmol	kJ/mmol	kcal/g
Glucose	From ACD-A (2.45% dextrose) and replacement and dialysate fluids (0–110 mg/dL)	198[a]	0.73	3.06	4 (3.4 if monohydrate)
Citrate	RCA of ACD-A (2.2% citrate) and TSC (4%)	192[b]	0.59	3.07	3
Lactate	Replacement and dialysate fluids	89	0.33	1.37	3.7

[a] *As glucose monohydrate.*

[b] *As citrate anion.*

RCA, Regional citrate anticoagulation; *TSC*, trisodium citrate.

TABLE 46.4 Composition of commercially available solutions for regional citrate anticoagulation.

	Hypertonic in sodium			Isotonic in sodium			
Citrate solution	**ACD-A solution (different manufactures)**	**4% Tri-Na citrate (Baxter)**	**Sodium citrate 4% (Fresenius)**	**Prismocitrate 10/2 (Baxter)**	**Prismocitrate 18/0 (Baxter)**	**PrismoCit 4K (Baxter)**	**Regiocit 18/0 (Baxter)**
Trisodium citrate (mmol/L)	74.8	136	136	10	18	10	18
Citric acid (mmol/L)	38.1	0	Not specified	2	0	2	0
Sodium (mmol/L)	224	408	408	136	140	140	140
Chloride (mmol/L)	0		0	106	86	114	86
Potassium (mmol/L)	0	0	0	0	0	4	0
Glucose (mmol/L)	124	0	0	0	0	0	0
Volume (mL)	500−1000	250−500	1000−1500	5000	5000	5000	5000

This metabolic load, commonly around 12−20 mmol/h, usually is rapidly metabolized through the Krebs cycle in the liver, skeletal muscle, and kidney, with the indirect production of 3 mmol of sodium bicarbonate for each 1 mmol of citrate. Indeed, in course of RCA the amount of bicarbonate derived from citrate metabolism provides the buffer supply to the patient, along with bicarbonate already present in the replacement and dialysis fluids. Commercially available RCA solutions may be classified on the basis of citrate concentration in *high-concentration citrate solution* (hypertonic in sodium) and *low-concentration citrate solutions* (isotonic in sodium) (Table 46.4). While the first ones are generally preferred in course of CVVHD and SLED, modalities mostly based on diffusive clearance, the low-concentration solutions can be used in course of CVVH, CVVHDF, and some variants of SLED (e.g., SLED-f). According to the principles of buffer balance in CRRT, the hypertonic solutions should be preferably combined with customized dialysis solutions characterized by low sodium and bicarbonate concentration, to avoid hypernatremia and metabolic alkalosis. In protocols adopting the isotonic citrate solutions, a high flow rate of the citrate-based fluid is needed to achieve the target citrate levels in the extracorporeal circuit blood and, as a consequence, citrate-buffered replacement solution will significantly contribute to the total dialysis RRT dose. In this regard, it is important to consider all of the possible electrolyte and acid−base abnormalities resulting from the fact that anticoagulation prescription for CRRT is strongly related to dialysis depurative effect. To achieve a correct balance, it is possible to combine the citrate solution with dialysis or replacement fluid characterized by adequate electrolyte and buffer concentration and, if needed, to provide an external continuous or extemporaneous supplementation. Several protocols of RCA are now routinely and safely applied in clinical practice, providing a CRRT prescription tailored on electrolyte and acid−base patient's status. As previously anticipated, the amount of energy delivered from fluids composition in course of RRT must be taken into account when estimating the nutritional needs of the patient with AKI. Indeed, independently of the kind of solution selected, citrate represents a source of energy, providing 0.59 kcal/mmol, which means approximately 150−280 kcal/24 h for a citrate load of 11−20 mmol/h [25,26]. Furthermore, by using Anticoagulant Citrate Dextrose Solution A (ACD-A), which contains 2.5% dextrose, an additional caloric load may derive from dextrose metabolism (0.73 kcal/mmol), delivering 350−600 kcal/24 h.

Implications for nutritional support

Energy requirements

The accurate determination of protein and energy needs is important in the clinical setting of AKI in the ICU, because both over- and underfeeding may occur, which are associated with poor outcomes [2,27]. In particular, significant underfeeding has been recently documented in a recent reanalysis of data from a large cohort of patients with AKI from the RENAL study, whose average daily calorie and protein intake was, respectively, 867 kcal and 34.8 g [28]. On the other hand, energy intake should never exceed actual energy requirements, since overfeeding is much more deleterious for critically ill patients than moderate underfeeding, particularly because of the increased hyperglycemia risk and insulin need, possible electrolyte disorders, and fluid overload [2]. In patients with AKI an energy provision of 40 kcal/kg/day via parenteral nutrition was associated with more severe metabolic complications, such as hypertriglyceridemia and hyperglycemia than lower intakes (30 kcal/kg/day), without any positive effect on nitrogen balance [29].

The gold standard for measuring individual caloric needs is represented by indirect calorimetry (IC), a noninvasive method allowing resting energy expenditure (REE) assessment based on oxygen consumption and carbon dioxide production measurements in the exhaled air [30]. In critically ill patients, REE measured by IC is in general considered for nutritional prescription. Unfortunately, IC measurements are not widely used in daily practice, even in the ICU setting [30].

Guidelines on renal and ICU patients [31–34] recommend the enteral route as the first choice for nutrition support in patients who are unable to eat, which is the case for the majority of ICU patients. Parenteral nutrition is indicated in AKI when the gastrointestinal (GI) tract cannot be used or when enteral nutrition (EN) is inadequate to reach nutrient intake goals. An energy prescription of 20–25 kcal/kg/day is currently recommended during the acute phase of the disease, and 25–30 kcal/kg/day during recovery. However, in many cases it is not mentioned if the actual, preadmission, or ideal BW should be considered. Considering that patients with AKI frequently have fluid overload and suffer sudden fluid shifts related to RRT, it is even more difficult to define the reference body weight (BW) to be used to estimate energy expenditure (EE) using predictive equations. A recent study in 205 critically ill patients compared the REE obtained using the Harris–Benedict equation using three different reference body weights (actual, ideal, and predicted BW) with REE measured by IC. It was found that REE estimated using the Harris–Benedict equation, regardless of the reference body weight used, did not agree with REE obtained by IC measurement, and Bland–Altman analysis showed wide limits of agreement [35]. Only two observational studies were performed in critically ill patients with AKI comparing IC determination of EE with EE based on kcal per kg BW and other predictive equations, including the Harris–Benedict equation [36,37]. Both studies agreed that EE calculation with formulas had low precision, wide limits of agreement and often under- or overestimate the true EE, depending on the BW used for the calculations. Thus despite being a very simple way to predict EE, this approach is likely to increase the risk of both over- and underfeeding in ICU patients with AKI.

Finally, whether only one IC measurement at the beginning of recovery is enough to tailor nutritional prescription during ICU stay is still an open question. In one study, there was no difference between energy measurements performed at the beginning of ICU stay and within 1 week, nor within 48 hours, despite a vast majority of patients (68%) presenting with differences greater than ± 10%, which could be clinically relevant [36]. A retrospective study on 1171 critically ill patients found a significant ($P < .0001$) between-day difference; however, the difference lost significance after excluding the first 2 days of hospitalization [38]. An expert position paper on IC in critically ill patients [30] stated that energy expenditure of critically ill patients is very dynamic and depends on the phase and the severity of illness, treatment, and extended bed rest. The same concept holds true for AKI patients [33,34]. Thus it is recommended that, whenever the clinical condition of the patient is changing, IC should be repeated.

Carbohydrate gain and loss during continuous renal replacement therapy

When prescribing enteral or parenteral nutrition in the ICU, clinicians should routinely assess for possible sources of “hidden calories.” Calories may be provided by dextrose-containing fluids administered via intravenous medications, during bolus or continuous crystalloid infusions, when using propofol or clevidipine for sedation, in addition to the potential energy gain via fluids used during CRRT. Except for propofol and clevidipine, which provide energy in the form of lipids, other “hidden sources” of energy derive from carbohydrates. Carbohydrates sources during CRRT are described in Table 46.3.

Depending on the protocol used, energy gain can be substantial. When standard modalities of CRRT with trisodium citrate solutions are employed, an estimated 300–500 mmol/day of citrate reaches the patient’s bloodstream, providing approximately 300 kcal/day [39]. However, during other modalities of CRRT based on the use of Anticoagulant Citrate Dextrose Solution A (ACD-A) as an anticoagulant and in some cases lactate as a buffer, the estimated daily energy load derived from the citrate, glucose, and lactate can range from 500 to 1200 kcal/day [26,40,41]. A recent study confirmed the potential caloric gain during CRRT [42]. Using a CVVH protocol based on the most recent guidelines on RCA, the average caloric uptake from CRRT was 513 kcal/day (218 kcal/day from citrate and 295 kcal/day from glucose). However, the impact of glucose-free replacement fluids was not assessed, which could actually have reduced the amount of caloric gain.

It is important to understand how the glucose content of fluids employed during CRRT may impact the delivery of extra energy. As a matter of fact, glucose-

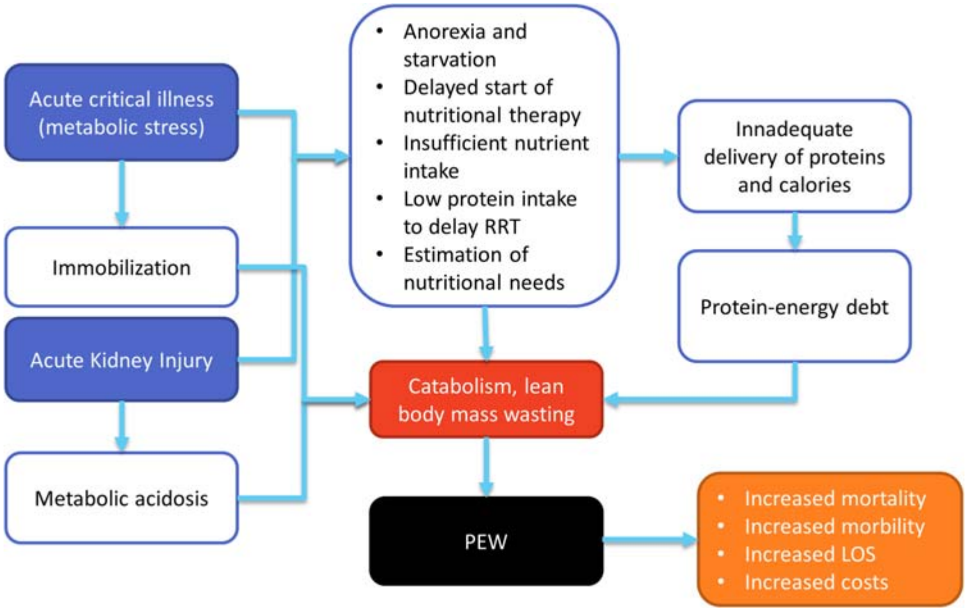
Acute critical illness (metabolic stress)
Immobilization
Acute Kidney Injury
Metabolic acidosis
Anorexia and starvation
Delayed start of nutritional therapy
Insufficient nutrient intake
Low protein intake to delay RRT
Estimation of nutritional needs
Innadequate delivery of proteins and calories
Protein-energy debt
Catabolism, lean body mass wasting
PEW
Increased mortality
Increased morbility
Increased LOS
Increased costs

FIGURE 46.2 Pathogenesis of muscle wasting in critically ill patients with AKI. *AKI*, Acute kidney injury.

free replacement fluids may contribute to glucose losses, since the lost glucose in the effluent is left unreplaced. On average, 40–80 g/day of glucose can be lost, if glucose-free CRRT fluids are used [43,44]. More important losses are usually associated with the use of higher effluent volumes and the presence of hyperglycemia and can significantly reduce the effective calorie delivered through the nutritional support [43]. In vitro models of different modalities of CRRT confirmed the effect that glucose-free fluids have on final glucose balance [45]. An equation was derived to calculate glucose losses for any method of CRRT when glucose-free fluids are used, and the blood flow rate is 200 mL/min:

$$y = 0.81\left[Q_D \times EC \times (G_{\mathrm{Pre}} - G_D) + Q_{UF} \times EC \times G_{\mathrm{Pre}}\right] + 4.16 \tag{46.1}$$

where y is the total kcal/day removed; Q_{D} is the dialysis flow rate (L/h); EC = 1 (extraction coefficient = E_{f}/Pre, where E_{f} is the concentration in effluent leaving the dialysis filter and Pre is the concentration in the prefilter blood); G_{Pre} is the glucose concentration prefilter (mg/dL); G_{D} is the glucose concentration in the dialysate (mg/dL); and Q_{UF} is the ultrafiltration rate.

The ideal fluid glucose concentration is unknown. In critical illness, intensive plasma glucose control (80–110 mg/dL or 4.4–6.1 mmol/L) with insulin leads to increased hypoglycemic events [46–49] and increased patient mortality [48], compared to conventional control (up to 200 mg/dL or 11.1 mmol/L). The target plasma glucose range is therefore recommended to be 144–180 mg/dL (8–10 mmol/L) [27,50–52]. In addition, CRRT is associated with an independent risk of hypoglycemia [53]. Using a fluid with a similar glucose content to optimal plasma level may help to prevent hypoglycemia and glucose variability, which are associated with increased mortality [54,55].

In conclusion, energy excess provided by RRT could be partially avoided by using protocols based on lower citrate concentrations [45], bicarbonate as a buffer, citrate solutions other than ACD-A in lower doses and without glucose [39], and glucose-free replacement or dialysate fluids. Alternatively, PIRRT modalities, such as SLED, easily allow increased citrate removal by the effect of diffusive treatment itself [56]. Notably, when citrate-based anticoagulation is not used, energy loss may occur when glucose-free fluids are employed and the glucose removed in the effluent liquid is not replaced. Also in any case, the energy excess provided by citrate, lactate, and glucose in RRT solutions should be factored in the patient's cumulative energy balance, and also for the purpose of glycemic control [27].

Proteins and amino acids

Critically ill patients in general and AKI patients in particular are characterized by an increased protein catabolism and turnover, with a redistribution of amino acids from lean body mass (mainly the skeletal muscle) to other tissues involved in the acute response, causing muscle wasting and negative nitrogen balance [2]. Multiple factors contribute to the increased catabolism of critically ill patients on CRRT (Fig. 46.2), the amino acid losses in the ultrafiltrate, and dialysis fluid being a key factor for worsening of this condition [2,43,57–63]. The

1. **TNA = UNA + other nitrogen appearance**
   - TNA: total nitrogen appearance over 24 hours
   - UNA: urea nitrogen appearance over 24 hours

2. **UNA = ($[UN]_{urine}$ x UV) + ($[UN]_{effluent}$ x EV) + change in body UN content**
   - $[UN]_{urine}$: urea nitrogen concentration in urine
   - $[UN]_{effluent}$: urea nitrogen concentration in CRRT effluent
   - UV: urine volume over 24 hours
   - EV: CRRT effluent volume over 24 hours

3. **Change in body UN content over 24 hours = $([BUN] \text{ x total body water})_{current\ day}$ minus $([BUN] \text{ x total body water})_{day\ before}$**
   - [BUN]: blood urea nitrogen concentration
   - total body water ≈ 0.6 x body weight (males) or 0.5 x body weight (females)

4. Other nitrogen appearance includes:
   - Amino acid nitrogen loss in CRRT (estimated 10% of TNA)
   - Creatinine nitrogen, other protein losses, skin losses, and gastrointestinal losses (not routinely measured)
   - UNA is thus estimated at 65–75% of TNA

   → **Therefore TNA ≈ UNA ÷ 0.7**

5. **Nitrogen balance = nitrogen intake – TNA**
   - Nitrogen intake = 0.16 x daily protein intake (nitrogen content of protein is about 16%)

6. Conversely to the above,
   PCR = TNA x 6.25
   - PCR: protein catabolic rate

The above equations are limited by the various assumptions, and serve only to provide a clinically useful approximation of nitrogen balance and protein catabolic rate.

FIGURE 46.3 Available equations for the estimation of protein catabolic rate.

factors related to the CRRT prescription, which will determine how many amino acids will be lost, include the modality of CRRT (convection, diffusion, or both), the blood and dialysis fluid flow rate, effluent rate, and membrane properties of the filter used [62,64]. In addition, many amino acids are low molecular weight substances with a sieving coefficient near 1.0; thus amino acids such as cysteine, arginine, alanine, and glutamine can be readily filtered from the blood into effluent [58,59]. Currently, with the increased efficiency of CRRT technology, allowing higher blood flow rates and increased effluent removal, it is possible to estimate that the actual amino acid losses of patients on CRRT are much more than those reported in the earlier studies [43,57–59,65]. In fact, a very early study that enrolled eight patients (four with cardiogenic shock and four with septicemia) reported a mean daily loss of 3.8 g/day of amino acids in septic patients and 7.4 g/day in patients with cardiogenic shock during CVVHF [57], while a more recent study in critically ill patients on CVVHDF reported a median amino acid loss of 13.4 g/day, ranging from 11.8 to 17.4 g/day, with ischemia being the most prevalent cause of AKI in 60% (6/10) of patients [65].

The optimal protein intake in critically ill patients with AKI is still unclear. It should be quantitatively sufficient to blunt skeletal muscle wasting, while providing the amino acids needed for the acute-phase response. Considering the increased loss of amino acids, patients on CRRT may require higher protein intakes [2,34]. Total nitrogen losses in a typical CRRT patient can reach up to 25 g/day [59,61], of which 10% is contributed by amino acid nitrogen loss [59], while the rest is likely to be derived from protein catabolism; this results in a negative nitrogen balance. Nitrogen balance in these patients can be improved by increasing protein intake [61,62]. Protein intakes up to 2.5 g/kg/day, at least in nonrandomized studies, led to near positive or slightly positive nitrogen balance; however, urea generation rate was highly increased [61,62]. A positive nitrogen balance is associated with improved patient survival in AKI with critical illness, but improved survival is not a direct effect of increased protein intake [62]. Nowadays, a protein intake of at least 1.3 g/kg/day is recommended for critically ill patients [31]. Nonetheless, it seems rational to increase daily protein intake by 10–15 g in patients on CRRT to compensate for the loss of amino acids (AA). Whether a higher protein intake is safe and leads to improved outcome remains to be shown.

One important consideration regarding protein intake prescription is that it is frequently normalized using the body weight of patients. Taking into consideration that critically ill patients with AKI frequently have fluid overload, the determination of the reference body weight to be used for protein prescription is a delicate issue. In fact, different body weights will lead to different protein needs estimation, and despite technical difficulties that may occur during 24 hours urine and dialysis fluid collection, it is very important to calculate the protein catabolic rate in critically ill patients with AKI. Equations to guide clinical estimations are shown in Fig. 46.3.

Since standard enteral formulas contain low amounts of protein (40–60 g protein/L), more concentrated disease-specific (renal) formulas containing 70–80 g protein/L should be preferred, with no reported difference in the prevalence of diarrhea in comparison to standard formulas [66]; in some cases, parenteral supplementation of amino acids is recommended to achieve protein intake goals [33,34,66].

Lipids

Effluent samples in CRRT are mostly lipid free, with trace amounts of cholesterol and triglycerides detectable, and there is no gradient for lipids across the hemofilter to suggest membrane adsorption [67]. Lipid homeostasis is not significantly affected by CRRT. The only nonnutritional lipid sources to consider in the ICU are related to the use of sedatives such as propofol and clevidipine. The first provides 1.1 kcal/mL in a 1% solution, while the latter provides an extra 2 kcal/mL [68].

On the other hand, lipid oxidation rate is increased, and glucose oxidation rate is decreased during AKI [69,70]. Because fatty acids are considered a key energy substrate in critically ill patients [33,34,70,71], a complete diet, including all of the macronutrients, is important to avoid essential fatty acid deficiency and to provide the right amount of calories. Lipids should represent at least 30%–35% of total energy supply. In the case of parenteral nutrition, patients should receive 0.8–1.2 g/kg/day of lipid from lipid emulsions, or as a part of the commercially available all-in-one total nutrient admixtures. Lipids should be infused over 18–24 hours, and serum triglycerides should be monitored, stopping lipid administration when triglycerides exceed 400 mg/dL or 4 mmol/L. Even though the use of parenteral medium-chain triglycerides (MCT) may result theoretically in lower serum triglyceride because of their faster oxidation, pharmacokinetic studies failed to show any clear advantage in terms of plasma clearance of triglyceride from the mixed MCT/LCT (long-chain triglycerides) lipid formulas compared with LCT-only emulsions. However, in a short-term crossover study in patients with AKI that were on RRT and total parenteral nutrition, MCT/LCT emulsions produced lower serum triglyceride levels than the LCT-only-based formulas [29].

Sodium and fluid balance

Because CRRT and PIRRT are RRT modalities running for prolonged periods of time, the net solute removal over time is higher than with intermittent hemodialysis, despite the lower rate of removal per hour. The most commonly adopted EN or parenteral nutrition (PN) formulas are generally hypotonic in sodium. Dialysis and replacement fluids are characterized by a sodium content of about 130–140 mmol/L, which generally provide the amount required to obtain an adequate balance. Hyponatremia in the course of AKI is often a manifestation of fluid overload, primary due to oliguria and other clinical condition associated with positive fluid balance (e.g., congestive heart failure) or worsened by the administration of a large amount of hypotonic fluid volumes in course of resuscitation therapy. In this context, the decision to start CRRT may be based on the necessity of a renal support also in the absence of other strict dialysis indications, interpreting RRT as an adjunct to enhance kidney function and allowing the administration of nutrition and drugs with limited concerns about concurrent fluid accumulation. As previously mentioned, in the course of CRRT in the setting of RCA, the presence of hypernatremia could be attributable to an inappropriate combination of high concentrated citrate solutions and dialysis solution. In this sense, CRRT constantly controls the net fluid balance providing a gradual ultrafiltration throughout the entire treatment period. Through a slow salt and water removal, these dialysis modalities allow a steady modulation of fluid overload also in hemodynamically unstable patients. Moreover, in AKI patients on CRRT and severe fluid overload, it is advisable to deliver an ultrafiltration rate per hour that permits to administer all the necessary therapies (such us parenteral nutrition or antimicrobials) without a risk of fluid accumulation.

Electrolytes and minerals

Although critically ill patients on CRRT are closely monitored with frequent laboratory tests, the onset of electrolytes abnormalities is not rare. In this sense a correct combination among the dialysate/replacement-fluid solutions, nutritional support, and micronutrients supplementation is strongly recommended to avoid laboratory and clinical complications.

Hypokalemia

Hypokalemia is a common complication of CRRT, described in up to 20% of patients undergoing CRRT [72]. The risk of its presentation is directly proportional to the dialysis dose [73] and may be further augmented with the use of low-concentration potassium solutions (Table 46.2), inadequate nutritional composition, or comorbidities (e.g., diarrhea, metabolic alkalosis, and diuretic therapy). By choosing CRRT solutions with a potassium concentration 4 mmol/L the risk of hypokalemia can be minimized, but if the imbalance persists, intravenous external supplementation may be needed. Potassium solutions such as potassium chloride or phosphate can also be easily added to enteral nutrition.

Hypo- and hypercalcemia

Alterations of calcium balance are quite uncommon among patients with AKI on CRRT, unless citrate is used as anticoagulant. As reported earlier, in course of RCA the infusion of calcium as chloride or gluconate is required to maintain ionized serum calcium levels within the normal range, especially when calcium-free dialysis fluids are used. Additionally, citrate accumulation, a potential complication of RCA with a reported incidence of 0%−12% [74], is associated with a fall in ionized calcium levels, as the result of impaired hepatic calcium release from the calcium−citrate complexes. A contemporary disproportionate rise of total systemic calcium concentration, represented by calcium complexed with citrate, may directly lead to an increase of the total-to-ionized calcium ratio (*calcium ratio*). In this setting the compromised citrate metabolism prevents bicarbonate generation, leading to negative buffer balance and metabolic acidosis. In the clinical practice a *calcium ratio* >2.5 is considered the critical threshold for an increased risk of impaired citrate metabolism [75]. In this regard, in clinical contexts at risk of citrate accumulation (e.g., severe liver failure and/or tissue hypoperfusion) monitoring of ionized calcium should be more frequent, and calcium ratio assessment carefully evaluated. With the exception of this peculiar condition, calcium abnormalities are routinely prevented by adjusting the calcium infusion.

Hypophosphatemia

Hypophosphatemia is a common electrolyte disorder in course of CRRT, especially when high RRT doses are delivered [72] and standard solutions are adopted [76]. Indeed, every prolonged modality of RRT provides a large removal of phosphate with the effluent, leading to a significant total phosphorus clearance [77]. Hypophosphatemia is associated with worsening respiratory failure with an increased risk of prolonged weaning from mechanical ventilation, cardiac arrhythmias, prolonged hospitalization, and increased mortality risk [78]. Considering the negative impact of hypophosphatemia on global patients' outcome [79,80], phosphate depletion in course of CRRT should be avoided. In this regard, the adoption of phosphate-containing solution has been reported to represent a safe and effective strategy to prevent CRRT-related hypophosphatemia [81]. Nowadays, several phosphate-containing CRRT solutions are commercially available, and they are used as dialysis and/or and replacement fluids also in the setting of RCA (Table 46.2). A close monitoring of phosphorus levels is essential during CRRT and, particularly when phosphate-free fluids are used, additional supplementation may be required. Phosphorus supplementation can be given via oral or intravenous route, infused intermittently, continuously, or added to parenteral nutrition. Especially in previously malnourished patients, additional phosphorus should be added to nutritional support, while caloric intake must be gradually increased to avoid the risk of refeeding syndrome [82]. This syndrome represents a possibly severe disorder in critically ills caused by the internal redistribution of phosphorus (and also potassium) into the intracellular compartment when calories are given to malnourished patients [83]. It seems to derive from the intracellular shift of phosphate mediated by insulin release and accelerated carbohydrate metabolism in response to the carbohydrate load. Finally, it is important to consider that the intravenous administration of phosphorus, if applied in the absence of a well-designed protocol and without strict monitoring, may increase the risk of further electrolyte abnormalities, such as hyperphosphatemia, hypocalcemia, and hypomagnesemia [84]. This approach is generally restricted to the cases of moderate-to-severe hypophosphatemia, or in the presence of symptoms.

Hypomagnesemia

Hypomagnesemia is a common disorder in critically ill patients with a reported incidence of 60%−65% [85]. In addition to the most known causes (such as diarrhea, malabsorption syndrome, chronic use of proton pump inhibitors and diuretics, hypercalcemia, and volume expansion), particular attention has recently been addressed to magnesium removal during the course of CRRT. In particular, the onset and the exacerbation of hypomagnesemia in the course of CRRT have been demonstrated to be associated not only with the depurative mechanism of RRT (diffusion or convective clearance), but also with the amount of ionized magnesium chelated by citrate and lost into the effluent, under the form of magnesium−citrate complexes. The majority of previously available dialysis solutions were characterized by low magnesium concentration (0.5 mmol/L) to correct hypermagnesemia, which are not indicated during the course of RCA. Indeed, during RCA performed with a low-concentration citrate solution, the use of dialysis/replacement fluids with a high magnesium concentration (0.6; 0.75; 1 mmol/L) could be indicated to prevent RRT-related hypomagnesemia. Given the increased mortality associated with hypomagnesemia/magnesium depletion, if these alterations occur, an exogenous supplementation may be required. Magnesium administration can be given via oral or intravenous route, the latter approach being preferred in the case of severe and/or symptomatic hypomagnesemia. A continuous or slow intermittent extemporaneous intravenous infusion of 2−4 g of magnesium sulfate can be administered during the course of CRRT.

Micronutrients

During critical illnesses, vitamins and trace elements may impact immunomodulation, wound healing and may have antioxidant properties [86,87]. Despite the fact that optimal dosing of micronutrients in critically ill patients is still a matter of debate, it appears quite clear that the start of CRRT in patients with AKI represents an additional variable negatively affecting serum micronutrient levels [88]. The depurative mechanisms on the basis of dialysis modalities along with a variable amount of hemofilter adsorption may increase the risk of vitamin and trace element deficiency, but dedicated and specific nutritional approaches are still lacking [89]. In patients on CRRT, a reduction in serum levels of vitamins C and E, zinc and selenium have been described, probably as a consequence of an increased utilization in critical illness [90,91] and loss secondary to CRRT. Specifically, daily losses in the effluent of about 68 mg of vitamin C, 0.3 mg of folate, and 4 mg of vitamin B1 (thiamine) have been reported [90,91]. The current suggestion is that the losses of selenium and other micronutrients in the effluent fluid should be replaced [92,93], and that these patients would need an additional amount beyond that provided by standard parenteral nutrition [91,94]. The optimal dose remains unknown, but a dosage of 100 mg/day has been suggested for vitamin C [95]. On the contrary, zinc, already present in some citrate solutions and replacement fluids, has been shown to be increased in serum after RRT start [63,91,96]. In conclusion, given the blood assay limitations and the lack of evidence of clinical advantages derived from micronutrients supplementation, no conclusive recommendations could be made.

Conclusion

Continuous or prolonged RRTs provide an unparalleled precise extracellular volume and uremic control in critically ill patients with AKI and have greatly facilitated nutritional support in this clinical setting. The available evidence suggests that CRRT and SLED can be important sources of energy. To avoid overfeeding, IC should be applied for the determination of energy requirements, while the amount of extra calories provided through RRT should be taken into account when prescribing nutritional support. Amino acid losses can be significant with prolonged modalities of RRT. Special considerations exist for volume and electrolytes management, which will mainly depend on the protocols and solutions used. Nutritional requirements should be frequently reassessed, individualized, and carefully integrated with RRT in patients with AKI. The adequacy and appropriateness of nutrition supplementation, especially protein intake, and the effect on protein energy—wasting risk and clinical outcomes, should be the target for future research in this field.

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CHAPTER

47

Motivating the patient with kidney disease to nutrition adherence and other healthy lifestyle activities

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Introduction

Patients with kidney disease are required to manage multiple nutritional and lifestyle changes and medical treatments to improve their health, including adherence to recommended diet and exercise routines, medications and health-monitoring activities, medical appointments, and in some cases, dialysis treatment. As kidney disease progresses, these demands increase and patients' motivation to meet them becomes more challenging. This diminished motivation may contribute to the patients' nonadherence and disengagement from their health-care providers. Helping patients with kidney disease implement and sustain necessary dietary plans, other healthy lifestyle activities, and medical regimens in collaboration with their nephrology team is critical for improving their treatment outcomes and quality of life. While treatment adherence for chronic illness involves many factors, such as patient demographics, treatment complexity and side effects, and availability of social and environmental supports [1], an important strategy to promote self-management is to activate the patients' motivation to manage their kidney disease [2].

This chapter describes an approach for enhancing patients' motivation for change, called motivational interviewing (MI) [3]. MI increasingly is being used in health-care settings to counsel patients with chronic diseases such as kidney disease [4,5]. The chapter reviews the basic principles and techniques of MI and the evidence to support the use of MI for improving self-management among patients with kidney disease.

What is motivational interviewing?

Miller and Rollnick offer a technical definition of MI as "a collaborative, goal-oriented style of communication with particular attention to the language of change. It is designed to strength personal motivation for the commitment to a specific goal by eliciting and exploring the person's own reasons for change within an atmosphere of acceptance and compassion" (p. 29) [3]. The approach is grounded in humanistic psychology, especially the work of Rogers [6], in that it employs a very empathic, nonjudgmental style of interacting with patients and presumes that the potential for change lies within everyone. MI is distinct from nondirective approaches; however, in that providers intentionally attend to and selectively reinforce patients' motives that support change [3,7,8]. The elements of (1) partnering with patients, (2) nonjudgmentally accepting their stance, (3) showing compassion, and (4) evoking the patients' own arguments for change collectively represent the spirit of MI. Over the course of the interview, providers help patients identify these change-oriented motives, elaborate upon them, and resolve ambivalence about change. If successful, patients become more likely to commit to changing their behaviors and initiating a change plan.

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Skilled health-care providers try to match their use of MI strategies to the patients' level of motivation. For example, a skilled provider can recognize when patients are motivated and ready to make changes and will move quickly to set a goal with patients. This is because extensive exploration of their motives for making a change might frustrate patients who are ready to move forward. In contrast, attempting to develop change plans with patients who are not yet committed to change will likely put patients in a position in which they might assert in words or in actions how they are not yet ready. This latter interaction illustrates how motives to change (called "change talk") and motives to stay the same (called "sustain talk") can be thought of as opposite sides of the same coin, meaning that if providers give insufficient attention to addressing important issues that impede change, patients are likely to raise these issues again during the interview [3]. Often providers expect patients who initially argue against change to have some intrinsic motivation for change within them. It is the responsibility of providers to look for opportunities to draw it out.

MI is best construed as a "conversation about change" (p. 12) that is designed to strengthen personal motivation and commitment to change [3]. In this regard, MI often is discussed within the context of the Stages of Change model by Prochaska and DiClemente [9]. The Stages of Change model posits that behavior change occurs sequentially across recurring stages. The earlier stages include precontemplation (patients are unaware or do not believe that there is a problem or need to change it), contemplation (patients are ambivalent about recognizing a problem and shy away from changing it), and preparation (patients are ready to work toward behavior change in the near future and develop a plan for change). The later stages include action (patients consistently make specific changes) and maintenance (patients work to maintain and sustain long-lasting change). Tailoring treatment strategies to achieve stage-related tasks is a hallmark of this model (e.g., conducting a cost—benefit analysis for someone contemplating change).

MI naturally fits into the Stage of Change model in that it can be used to help move patients from one stage to another, especially in the early stages of the model [10]. Patient-centered counseling skills may build rapport and engage patients who are less motivated to change. Eliciting additional change talk might lead ambivalent individuals to conclude it is relatively worth it for them to change rather than to not address areas critical to their health and quality of life. Working with patients to identify steps they can take might help them feel more prepared to initiate a change plan. In later stages, MI strategies are useful for attending to wavering motivation as patients take action or try to maintain changes in stressful situations. Finally, the Stages of Change model illustrates how MI integrates well with other treatment approaches that are more action-oriented. For example, MI might be used to engage patients in kidney disease education and skill-building activities (e.g., meeting with a dietitian to learn how to consume the right balance of protein) or in other treatments for comorbid conditions (e.g., cognitive behavioral therapy for depression) [11].

MI emerged out of early efforts to establish brief interventions for alcohol problems [12]. These interventions shared a harm reduction approach in that they aimed to help patients move toward reduced drinking to lower risks rather than to automatically advocate for total abstinence as the only acceptable goal. Common components of these brief interventions, as represented in a FRAMES acronym, were Feedback, emphasis on personal Responsibility, Advice, a Menu of options, an Empathic counseling style, and support for Self-efficacy. With FRAMES as a guidepost, William Miller and his colleagues developed the "Drinker's Check-up" in which patients received feedback about their drinking relative to population or clinical norms and then explored what it might suggest about their drinking and motivation for reducing or stopping it. Early studies found the Drinker's Check-up to be quite effective [12]. Given this success, MI with personalized assessment feedback then became adapted into a more structured and manualized format and termed motivational enhancement therapy or MET [13].

As applied to the management of kidney disease, the harm reduction stance of MI implies that the aim of MI is to help patients prepare themselves to make changes in any behaviors that might positively impact their kidney disease. Determining what areas matter most to them (e.g., diet, exercise, and medication), which areas they believe they can change (e.g., limiting fluid intake, increasing activity level), and what goal to achieve (e.g., walking 15 min/day) is more important than pushing them to commit to something they may not want to or feel able to achieve, even if full adherence would have obviously better health outcomes.

Implied in the previous discussion is that MI is behaviorally specific and has direction. This means that providers need to be clear about what it is that they are trying to motivate patients to do or to change. Motivation for change in one area does not guarantee motivation for change in another (e.g., a patient may commit to taking a phosphorus binder but not agree to substantially limit foods high in sodium). Each behavior may require a separate motivational enhancement process. MI also requires that providers take a stance about the preferred direction for change. For many behaviors related to kidney disease, this decision is relatively clear in that most patients would agree that it is ethically sound to enhance motivation for changes that decrease morbidity and mortality, such as blood glucose control or smoking cessation. However, some behavioral issues involved in kidney disease care do not have a clear change direction. For example, decisions about whether to start end-stage renal disease therapy with peritoneal dialysis or hemodialysis or proceed with a preemptive kidney transplant likely would require a nondirective approach in which providers suspend their own values or goals and assume a position of "equipoise" (i.e., indifference or no clear attachment to a position or recommendation). In these situations a patient-centered counseling approach, devoid of evocation, would allow patients to explore their ambivalence without intentional provider influence.

What is not motivational interviewing?

For clarification purposes, it is helpful to consider what MI is not [7]. As noted earlier, MI is not based on the Stages of Change model, though it is complementary to it. Stages of Change is more of a comprehensive way of thinking about how patients change, whereas MI is a clinical method that helps patients prepare for change. Likewise, MI is not cognitive behavioral therapy. The latter approach supplies patients with education and coping skill development and encourages the repeated practicing of these skills to better manage their problems. MI is fundamentally humanistic, not behavioral, in origin in that it elicits the patients' motivations for change rather than putting in place what is missing (knowledge and skills). MI also is not a way of manipulating others or making them change when they do not want to. Behavior change in MI is born out of a person's intrinsic motivations. Health-care providers can only call forth motivations that already exist within patients; they cannot impose the concerns or wishes of others when an individual does not see these issues in his/her best interest. Finally, MI does not require that providers conduct a decisional balance or give personalized feedback. These are techniques that often are helpful for eliciting change talk, but they are not essential to the conduct of MI, and they often are used in other treatment approaches. In this regard, MI is not a series of techniques but rather a way of being with patients in which guiding attitudes and practices orient the patient toward change.

Four motivational interviewing processes

There are four processes that comprise MI: (1) engaging; (2) focusing; (3) evoking; and (4) planning, with each process often overlapping with each other. Miller and Rollnick define engaging as, "the process of establishing a mutually trusting and respectful helping relationship" (p. 40) [3]. In the engaging process the provider seeks to establish a partnership by facilitating the patient's story using fundamental MI strategies (e.g., open questions, reflections). In doing so the patient can share his or her perspective, and rapport is cultivated within the dyad.

Focusing is "an ongoing process of seeking and maintaining direction" (p. 94) [3] by identifying areas for exploration in treatment. These areas are determined through a combination of the patient (e.g., focusing on improving dietary changes), the setting (e.g., dialysis clinic), and the clinical expertise of the provider (e.g., improve anhedonia that is interfering with treatment engagement). Listing agenda items on paper and helping the patient prioritize them is a hallmark strategy used to focus the interview on specific behavior change targets (see the "Other useful strategies" section).

Evoking is the third process in which the provider tunes into the patient's language that favors change (change talk) and applies strategies to generate change talk if not readily offered by the patient. There are several ways for providers to evoke change talk as outlined in Miller and Rollnick [3], including but not limited to (1) eliciting what the patient knows, providing information, and eliciting the patient's reactions to the information; (2) using open questions and reflections to further change-oriented discourse; (3) assessing and exploring the patient's importance and confidence related to making changes using a numeric scale; and (4) engaging the patient in a decisional balance activity to explore the benefits of change and the costs of not changing. These strategies can be used in traditionally briefer medical encounters and applied by members of the patient's interdisciplinary care team, making them ideal for multispecialty settings.

Finally, the last process is planning, where the patient identifies a self-prescriptive behavior change goal. It is described as "developing a specific change plan that the person is willing to implement" [3]. Often, a patient is ready to transition to planning when the frequency of change talk has increased and indicates that the patient is ready to prepare for change. This includes expressing commitment to change, activation or readiness around change (e.g., pondering potential options to facilitate change), and taking initial steps to initiate behavior change. During this stage, providers assist patients in setting the change plan that includes anticipating obstacles, identifying supportive others, and reaffirming their commitment to change. If the patient voices ambivalence during the planning process, providers explore it rather than pushing to complete the plan when the patient has backtracked motivationally.

Strategies

While MI is a style of being with others rather than merely an application of techniques, MI incorporates several strategies that operationalize how providers use MI [3]. These strategies include (1) those that are fundamental to the approach and used throughout the MI processes, such as open questions, affirmations, reflections, and summaries (known as OARS) and (2) direct methods for evoking change talk. The continuous interplay of fundamental patient-centered strategies and direct methods to elicit and reinforce change talk is essential to conducted MI proficiently. In addition, other useful strategies can help patients prioritize behavior change issues and allow for a collaborative exchange information between patients and providers.

Fundamental strategies: open questions, affirmations, reflections, and summaries

Fundamental strategies are a mainstay of MI in that they help providers understand the patients' perspective, convey empathy, and build a positive relationship with their patients. As the conversation unfolds, health-care providers attend to the balance of statements made by patients that support or thwart behavior change (i.e., change vs sustain talk) to gauge the patients' level of motivation and adjust their use of MI techniques accordingly. Open questions encourage patients to talk more and may be used to strategically draw out motivations for change (e.g., "What would be good about quitting smoking?"). They stand in contrast to closed questions, in which providers seek specific information (e.g., demographics, history, and symptoms), often with questions that can be answered with a "yes" or a "no" response. For example, a patient's positive response to the closed-ended question, "Have you been sticking with the diet we discussed last time?" would provide some useful information. However, he or she would not have fully elaborated on adherence to various aspects of the dietary plan, which an open question (e.g., "What parts of your plan have you been able to stick with since we last met?") might have elicited.

Affirmations (i.e., acknowledgment of a person's strengths, attitudes, and efforts that promote behavior change) build collaboration between providers and patients and promote self-efficacy. Sometimes this entails reframing a behavior in a manner that helps patients see it in a more positive light. For example, a provider who has a patient who becomes dismayed by his series of self-monitored high blood glucose readings might say, "You're keeping a close eye on your blood sugar to get it under better control."

MI also relies heavily on the skilled use of reflective listening in which providers restate or paraphrase their understanding of what patients have said to express empathy, as well as to bring attention to ambivalence, highlight change talk, and explore and lessen language that supports the status quo. In MI, reflections are "simple" when a provider essentially repeats what the patient has said and "complex" when the provider articulates new meaning implied by the patient's original statements. Complex reflections demonstrate a deeper understanding of the patient's experiences. As an example, a provider asks a patient with kidney disease, "How have things been going with dialysis?" The patient responds by saying, "What difference does it make?" A provider could use a simple reflection to encourage more discussion about the patient's expressed skepticism ("You're not sure dialysis makes a difference"). A complex reflection would capture the patient's implied demoralization and show more empathy ("You seem pretty discouraged").

Summaries provide opportunities for providers to demonstrate fuller understanding of their patients' experiences and help them consider the bigger picture of their motivations for change. Summaries also allow providers to collect multiple change talk statements as a strategy to enhance motivation, link discrepant statements that capture ambivalence, and shift focus to other behavioral areas (e.g., move from discussing medication adherence to exercise). The following is a dialog that ends in a summary statement. Use of fundamental strategies is italicized.

Provider: How have you been doing? (*open question)*

Patient: Not too well actually. I have been having several annoying problems.

Provider: You sound frustrated. (*complex reflection*)

Patient: I am really frustrated. [pause] Sometimes I feel like not even bothering with this treatment.

Provider: It is a lot to handle. (*complex reflection*) Tell me about the problems you've been having. (*open question/request*)

Patient: Well first of all, I've been having a lot of muscle cramps. They are mostly in my legs and they are quite painful. I get them especially when I sit around for awhile and sometimes when I am sleeping; they wake me up and I have to walk them off. The other thing is itching. It drives me crazy. I am scratching myself all the time. Between the cramps and the itching, I feel like I am being attacked from inside and outside. Is there anything we can do about it?

Provider: There are several things that are possible. Muscle cramps and itching are common for people with kidney disease. However, the causes may differ among people. We will have to talk a little more about it. I also will want to check your blood level of phosphorus and a hormone called PTH that can lead to itchy skin. (*patient-centered feedback*)

Patient: Alright. There is one more thing. I also feel tired most of the time. Sometimes I wonder if I am getting depressed.

Provider: You are not sure if you are tired because of the kidney disease or if it is due to being depressed over having to deal with the disease. (*complex reflection*)

Patient: Yeah. Sometimes it is hard to make sense of things. I guess I am hoping that you can help me figure things out.

Provider: It is confusing, and I certainly hope we can work together to figure it out. (*simple reflection that builds collaboration*) I really appreciate how you're being open about what you're experiencing (*affirmation*).

Patient: Well, I really don't have anyone to talk to about what I am going through. Sometimes I want to forget all about it and give up. Other times, I try to be strong and positive and do everything I can to delay having dialysis. It's such a battle – one that I fear I might be losing.

Provider: And it might feel that way because there is a lot on the field. You've been having painful leg cramps, lots of itchiness, and you are beginning to feel depressed by it all. Nonetheless, you're still trying to work with us and find ways to address these problems. You haven't given up (*summary; affirmation*).

Direct methods to evoke change talk

Direct methods for evoking change talk hinge on the capacity of health-care providers to recognize how patients talk about change [3,8,14]. Change talk is embodied in the acronym DARN-CAT (see Table 47.1). DARN (desire, ability, reasons, and need) is sometimes referred to as preparatory language in that these statements motivational factors prepare patients to commit to change [14]. Desire statements indicate a clear wish for change ("I don't want my kidney disease to get worse"). Ability statements indicate patients' beliefs that they can change, given their skills and available resources ("I used to swim, and there is a YMCA in my town that I could go to"). Reason statements note the benefits of change and the costs of not changing ("I will feel better" or "If I stop drinking soda, I might get my blood sugar under better control"). Need statements underscore how the problem behavior interferes with important areas of an individual's life and how changing the behavior would likely improve matters ("I don't want to be the next person in my family to die from kidney disease" or "I certainly want to teach my kids how to live a healthy life to prevent this from happening to them").

TABLE 47.1 Change talk categories: DARN-CAT [33].

Category	Definition
Desire	Statements that indicate a clear wish for change
Ability	Statements that indicate patients' beliefs that they can change
Reason	Statements that note the benefits of change and the costs of not changing
Need	Statements that underscore how the problem behavior interferes with important areas of a patient's life and how changing the behavior would likely improve matters
Commitment	Statements that convey a patient's intention to change
Activation	Statements that indicate how patients are getting ready to change
Taking steps	Initial demonstration of behaviors that would support change

CAT (commitment, activation, taking steps) represents statements that suggest patients are mobilizing themselves for change. Commitment statements convey the stated intention to change ("My quit date will be this Thursday"). Activation statements indicate how patients are getting ready to change ("I am going to fill the prescription at the pharmacy right after I leave here"). Statements about taking steps to change are the strongest demonstration of commitment in that the patients have put their words into action and are reporting these early efforts to the provider ("Instead of going out to drink after work, I went to the gym and exercised").

During the interview, providers identify the extent to which patients express motivation in each of these areas, use their fundamental skills to support and develop patients' change talk and have them elaborate further, and in a goal-oriented fashion, directly attempt to evoke motivation for change. MI offers multiple techniques for these purposes. Some options are described next:

1. Evocative questions—directly asking open questions to elicit change talk (e.g., "In what ways do you

think you can better manage your kidney disease?" [evoking ability to change] "How would things be better for you if you followed the recommended diet?" [evoking reasons to change]).

2. Readiness rulers—asking patients to rate themselves from 0 to 10 about the importance of and their confidence in changing a specific behavior related to their kidney disease and following up with evocative questions designed to elicit change talk (e.g., "How come you said a *5* rather than a *0*?" "What would it take for you to go from a *5* to a *6*?").
3. Looking forward—asking patients open questions to look to the future at some time interval (e.g., 5 years from now) and consider where their lives might be headed with and without healthy lifestyle changes (attempting to reveal potential reasons or need to change to enhance the importance of change).
4. Exploring goals and values—inquiring about what matters most to patients (e.g., being a good parent or available grandparent, independence) through reflections and open questions and how the targeted behavior fits with these goals or values (e.g., "The thought of being tethered to a dialysis machine is unacceptable to you. How would being more physically active affect your level of independence?").
5. Past successes—exploring past periods when patients were successful in some areas and how they might import these experiences into their current circumstances ("It's great that you were able to stay on top of your diet by tracking the foods you ate; keeping it up for several years is impressive. What helped you be successful then? How can those strategies work for you again?").

Other useful strategies

Kidney disease management typically requires simultaneous attention to several behavioral issues (e.g., diet, exercise, medication adherence, adherence to the dialysis treatment regimen, blood glucose control, blood pressure control, phosphorus control, smoking cessation, comorbid depression, or anxiety), and this reality often is overwhelming to patients and their health-care providers during any one appointment where time is limited. Providers can use a simple agenda setting chart in which they record the pertinent behavior change issues on paper and have patients indicate which of them they want to discuss during the interview [14]. It is important that these priorities be put in the context of the concerns the provider has about the patient's medical status. For example, if a patient is poorly compliant with the dialysis treatment regimen but wants to focus on his minimally elevated phosphorus level, the provider will need to organize the conversation appropriately to share concerns about treatment adherence while simultaneously addressing the patient's priorities.

Education, advice-giving, and direction are commonplace in the health-care settings, particularly because providers' often have a natural tendency to try to fix patients' problems (referred to as the "righting reflex") [3]. When patients have not solicited professional input, however, they may not be receptive to it. Instead, providers ask permission to provide information or advice and employ an elicit−provide−elicit (or ask−tell−ask) technique in which providers (1) elicit from patients what they know about the topic being discussed, (2) provide information as needed, and (3) elicit patients' reactions to the shared information [4]. For example, a provider may wish to recommend that a patient meets with a dietitian. Instead of providing the recommendation in an unsolicited manner, the provider would first ask the patient about his or her past experiences with dietitians and then, with permission, talk about how a dietitian might be helpful to the patient and conclude by getting the patient's reaction. This technique promotes collaboration and reduces the chance that patients experience their providers as lecturing or telling them what to do.

The following conversation between a provider and his patient demonstrates the use of several strategies (italicized) described earlier:

Provider: When we last met, we reviewed some recommended changes to your diet because your blood pressure was elevated. What is your understanding of your blood pressure right now? (*Elicit)*

Patient: The nurse said that it was 155 over 95, which is better than what it had been.

Provider: Those numbers are correct! We would like to see that top number safely below 130 which means your blood pressure today is on the high side. (*Provide)* Last time we talked about reducing salt in your food. How did it go?

Patient: Not that well. I tried to cut back on salt, but I don't like how things taste if they aren't seasoned.

Provider: Even though you like the taste of salt, you still tried to reduce how much you use *(Affirmation)*. How come? (*evocative question*)

Patient: I was worried about my health, and I want to see my granddaughter graduate medical school. You said my blood pressure was high and that it increased my risk for all kinds of problems, especially heart problems. Did you say my blood pressure is still high?

Provider: Yes. It is 155 over 95, which is higher than our target needed to keep you safe from other health risks like cardiovascular problems, like heart attack or stroke. (*Provide*) You mentioned feeling an urgency to stay healthy so you can celebrate your granddaughter’s achievements. What are your thoughts about how your diet may be impacting your blood pressure? (*Elicit*)

Patient: It’s just so hard to eat foods that taste bland and even more difficult figuring out what I can eat at a restaurant. I’m really upset with myself that I can’t seem to control what I put in my body.

Provider: And you fear that if you don’t begin to find ways to reduce how much salt you eat, you may even risk not being able to attend your granddaughter’s graduation. (*exploring goals and values*, *looking forward*)

Patient: That’s the worst of it. My granddaughter is working so hard to become a doctor, and I’m having trouble doing what the doctors tell me to do.

Provider: You’d like to better manage your health for yourself and your granddaughter. Finding ways to cut back on salt is very important to you. (*exploring goals and values*)

Patient: Yes. I just keep running into the same problems. Food just doesn’t taste good without salt.

Provider: So how can you make food taste better without eating too much salt? (*evocative question*)

Patient: Well, I could cook with more spices and use more fresh food rather than canned foods or frozen dinners.

Provider: You have some good ideas (*affirmation*). Can I share with you another idea that some people have found helpful? (*asking permission*)

Patient: Sure.

Provider: What are your thoughts about meeting with the dietitian to help you discuss other ways of sprucing up your meals? (*evocative question*)

Patient: Sure. I thought I could just do it on my own, but I think I need some help learning how to cook in a different way.

Use of a decisional balance activity (i.e., exploring the costs and benefits of changing and not changing) is common in MI [3]. This activity provides a structured method for understanding the basis of a patient’s ambivalence in that the benefits of change (“I’ll delay the need for dialysis for many years”) and the costs of not changing (“If I don’t change how I eat and exercise, a heart attack may kill me before my kidney disease does”) provide reasons to change, whereas the benefits of not changing (“A person has got to have some pleasure”) and the costs of changing (“Healthy food is expensive”) provide reasons to remain the same. By strategically eliciting more reasons for change and, to the extent possible, resolving reasons to remain the same (e.g., identify some healthy foods that taste good and are affordable), a provider might help the patient tip the balance toward change. However, it is recommended that the use of decisional balances be applied with caution. In a 2013 study, Miller and Rose found that the use of decisional balances with clients who were ambivalent ultimately decreased the decision to change [15]. They suggest that the use of decisional balances be reserved for clients who have already decided to change, which can strengthen their commitment. They recommended other evocation strategies, like some of the direct methods described earlier, may be more effective in resolving ambivalence.

Another important skill is how to gauge patients’ readiness to change and transition from the evoking to planning for change. Providers typically recapitulate what patients have said, especially those statements that suggest how they are now ready to change. Following this summary, providers then pose a key question to solidify commitment to change (“What’s your next step?” or “From what you’ve told me, how do you want to proceed?”). Miller and Rollnick have used the analogy of a person as a skier standing at the summit (assisted up the mountain by the provider) [3]. The key question provides a supportive nudge that helps the person go down the mountain.

Change planning is a strategy that providers use to negotiate a plan with patients about how they will change their behavior [3]. Critical to this process is maintaining a patient-centered stance in which the plan is derived by the patient, with the assistance of the provider, rather than the provider becoming prescriptive at this point. Providers ask patients to set their targeted behavior change goal (“I am going to monitor my blood sugar once a day”), describe steps they will take to change (“I will test it in the morning before I eat my breakfast”; “I will record my level each day on my monitoring form”), identify who might support them and how (“I am going to ask my wife to review my sugar levels at the end of each week”), anticipate obstacles (“I travel once in awhile and need a way to not forget to take my glucometer with me”), and reaffirm their commitment to the plan. If during the process of mobilizing their commitment, patients become uncertain again (the cold-feet phenomenon), the provider reflects this ambivalence rather than trying to press through it and provides another opportunity to revisit the plan in the current meeting or at another time. Being in a hurry to complete the plan when patients are not ready is a common trap into which providers fall.

Handling sustain talk and discord

Previously known as "resistance," sustain talk refers to a patient's statements about what maintains the target behavior, whereas discord refers to challenges within the interpersonal dynamic between the patient and the provider [3]. This revision in language was made in response to concerns that the word "resistance" insinuated a sense of patient-driven opposition or pathology and excluded the interpersonal dynamic between the provider and patient that may be contributing to the disconnect [3].

Sustain talk conveys the patient's intent to make no changes to behavior. The patient may offer reasons for maintaining the behaviors ("Eating a lot relaxes me") or the difficulties of trying to change them ("I can't resist the urge to smoke"). Sustain talk in this context informs providers about dilemmas faced by individuals, thereby providing opportunities for addressing obstacles to change. Some strategies for skillfully handling sustain talk include (1) simply reflecting the sustain talk to show empathy and better understand the issue ("You don't believe you should have to make any further changes in the way you eat when you feel you have made big changes elsewhere" in response to a patient who says, "I already take the meds, cut back on soda, and started walking after work. I don't want to change my diet anymore"); (2) amplified reflections to determine the degree of commitment to a discordant statement ("Your wife has no basis to be concerned about your weight" in response to a person who complains how his wife pesters him about his obesity); (3) double-sided reflections to pair the sustain talk with other things said that favor change, thereby introducing some ambivalence back into the conversation ("You feel like stopping the medication now that you have changed your diet and exercise, and you worry that if you do, you might develop hypertension again"); and (4) emphasizing personal choice and control to assure the patients that it is they who determine what they will do, not others ("Dialysis is not easy, but it is manageable and you have a few options about how to do it. We will work with you to determine what the best way is to go about getting dialysis, and ultimately it is your decision").

Miller and Rollnick describe discord as "smoke alarms" or "a change in the air" to alert providers that there has been a shift in the working alliance [3]. They describe patient behaviors such as defending themselves through external blaming or justification, squaring off with a provider (i.e., "You don't care, don't know, have no idea etc."), interrupting, and disengaging from the conversation as examples of discord. In using MI, a provider avoids adopting a confrontational, authoritative, warning, or threatening tone (all inconsistent with MI), which might cause the patient to become even less engaged in treatment [14]. These behaviors can originate from the patient, well before the visit begins, or discord can arise during the visit (and often unintentionally provoked by the provider). Provider behaviors such as using labeling language (e.g., alcoholic, diabetic), disagreement over which behaviors to focus on, overcorrection of patient's beliefs and perspectives about change, and prematurely pushing toward planning can generate discord within the interaction. Strategies for navigating discord include affirming patient's strengths and effort which can attenuate defensiveness. Additionally, shifting the focus on the conversation away from the activating topic can bring patient and provider back in sync on their shared goals for treatment. For example, a patient stating, "You don't think I'm trying hard enough, do you?" in response to a provider assessing importance. In response, the provider might say, "When I asked about how important you feel it is to make changes to your diet, it felt like a judgment. My goal is to learn more about the things that are important to you versus me falling into a trap of imposing my values onto you. Perhaps we can talk about all of the ways that you've been working hard to make changes to your diet." Alternatively, simply apologizing, "I'm very sorry. I didn't mean to sound judgmental" can help mend fractured rapport when experiencing discord with a patient.

Successfully managing kidney disease is difficult for several reasons. As described earlier, patients must continuously manage numerous medical treatments (scheduled appointments, dialysis regimens, prescribed medications, and health-monitoring activities) and address several nutritional and other lifestyle changes to treat their kidney disease and associated comorbidities. These demands on patients increase as their kidney disease progresses, and their motivation to meet them typically fluctuates over time. Providers who use MI with patients understand that sustain talk is more of a reflection of what makes change hard for them rather than as a refusal to change or mere ignorance. The former perspective promotes empathic and supportive provider–patient interactions. The latter one might lead providers to label patients as "unmotivated" and confront, warn, or lecture them, thereby, risking putting patients in a position of defending themselves by arguing for their status quo behaviors [16].

The next dialog demonstrates the use of MI strategies for handling sustain talk and discord (italicized in text) with a dialysis-dependent patient who needs to lose weight to become eligible for a kidney transplant.

Provider: I'd like to talk with you about your weight if that's okay with you? (*emphasizing personal choice and control*)

Patient: Sure, but I already know what you are going to say.

Provider: You're concerned I'm going to give you a lecture rather than try to understand what makes losing weight difficult for you. (*reflection*)

Patient: Well I know what I must do and I've tried it all before. It's just so hard now with all these adjustments to my diet, and I'm too tired to move around like I used to.

Provider: So having tried everything and being so exhausted, you feel like there is nothing you can do about your weight. (*amplified reflection*)

Patient: That's not what I said. I just don't feel I can do it on my own. You're putting words in my mouth.

Provider: My apologies. I missed the mark on describing your thoughts about your diet. (*apologizing*) Perhaps we can explore what would help you be successful with making changes to your diet. (*shifting focus*)

Patient: It's like I need a coach or something to help me, to point me in the right direction and keep me going. I'm worried about it because I want to get the kidney transplant.

Provider: So your diet is somewhat complicated and tiredness gets in your way. On the other hand, you want to go to the kidney transplant evaluation knowing you meet the criteria, which requires that you lose weight to be listed. You feel you might be able to lose weight if you had someone to coach you along the way. (*double-sided reflection*)

Patient: Yeah. Could I get someone like that to help me out?

Provider: Sure. There are a few options. You could meet with the dietitian regularly, and she can serve as a coach. We also have a weight control program right here, that I can refer you to. Program counselors work closely with you to help you lose weight. Another option is for you to go to a program in the community, like Weight Watchers or others, if you don't want to come here. If these approaches don't work, then we can consider medication or surgical options, but it would be best to first try to improve your eating and exercising, especially since you will need to improve these areas anyway to increase the chance that kidney transplantation succeeds. What do you think? (*emphasizing personal choice and control*)

Patient: What's the program like here?

Empirical support

Several systematic reviews and meta-analyses [17–20] have examined the large body of MI research to determine *if MI works* across a wide range of problem areas (e.g., alcohol, tobacco, illicit drugs, diet/exercise, treatment adherence/engagement, blood pressure, weight loss, smoking and substance use, and physical activity). A recent systematic review of 104 narrative reviews and metaanalyses of MI treatment outcome studies suggests that the evidence for beneficial effects of MI is strongest for reducing binge drinking, frequency and quantity of alcohol consumption, substance abuse in people with dependency or addiction, and increasing physical activity participation [21].

Along with questions about the effectiveness of MI come concerns about the speed in which effects are observed. Arguably the busiest setting, a meta-analysis examining the application of MI in primary care, found MI to be useful in promoting health-related behavior change in as few as one session [21]. Additionally, Lundahl and colleagues examined 119 studies and found MI to successfully produce behavior change, but in less time, compared to other interventions [18]. MI also significantly increased patients' treatment engagement, with effects being durable, lasting up to 1 year.

The effectiveness of MI delivery systems outside of face-to-face interactions has also demonstrated effectiveness. Previous research suggests that face-to-face modalities of MI-based interventions are more effective than those delivered by phone [22]; however, in recent years, more studies have emerged regarding the acceptability and feasibility of computer and web-based platforms [23,24]. There has been some success with computer-based MI interventions for adults related to initiating substance use treatment after a 2-month follow-up [25], and also related to weekly minutes of moderate and vigorous physical activity [26]. Randomized trials related to postpartum substance use have demonstrated efficacy and acceptability of electronic "screening, brief intervention and referral to treatment" (SBIRT) models that utilize MI [27,28]. Other studies have also found equivalence between electronic SBIRT and clinician-delivered SBIRT models where both included the same amount of MI principles [29].

MI is also effective for changing health behaviors across the developmental lifespan. A 2014 meta-analysis conducted focused on adolescent health behaviors (such as risky sexual behavior, physical activity, and diet) demonstrated short-term post-intervention effects that were maintained, on average, 8 months after the intervention concluded [30]. Among middle-aged and older adults, MI has demonstrated effectiveness in reducing episodes of unprotected sex following a four-session, telephone-delivered MI intervention [31]. Health promotion and disease prevention efforts among older adults are also benefitted by MI, particularly with increasing fruit and vegetable consumption, physical activity, glycemic control [32].

Studies examining *how MI works* have supported the underlying theory of MI. Miller and Rose provide a helpful summary of this literature [8]. In brief, these studies have shown that providers who adhered to MI, in contrast to those who did not, were more likely to have patients who became more motivated to change and, in turn, had improved treatment outcomes (e.g., reducing drinking, meeting dietary goals, increasing activity level) [33–42]. A 2018 meta-analysis of MI process studies found that when providers use a higher proportion of MI consistent strategies, their actions are likely to result in patients who use proportionally more change than sustain talk [43]. Higher proportion change talk, in turn, was related to reductions in risk behaviors at follow-up. MI inconsistent behaviors were correlated with more sustain talk. Independent of other effects, more sustain talk was associated with worse outcomes. This meta-analysis suggests that MI works well when providers perform it well (i.e., with adherence to its principles and strategies). Getting sufficient training and supervision to learn MI is imperative (see the “Learning motivational interviewing” section).

Furthermore, nuances in the frequency and movement in change talk (i.e., toward change, away from change) appear to impact clinical outcomes. One study found that ending treatment sessions when in a “toward change” position resulted in less alcohol consumption (13 drinks) per week when compared to sessions that ended with “away from change” [44]. Most notably, Glynn and Moyers [45] employed an applied behavior analysis design to intentionally increase or decrease the amount of change talk, with success. This finding suggested that even within the absence of other MI skills, evoking change talk specifically may be a critical strategy to any behavior change intervention [45].

Applications in kidney disease management

MI has been successfully adapted for use in healthcare settings to manage chronic disease, including diabetes. Several studies have shown that MI can be an effective method of working with teenagers and adults with diabetes, producing improvements in glycemic control, psychological well-being, and quality of life [46–48]. MI also has moderate-to-strong effect sizes for a variety of health-related behaviors involved in the management of chronic kidney disease (CKD), such as healthier eating [49–52], increased physical activity [49,53,54], improved blood pressure control, weight loss [49], better medication adherence [55], and better glucose self-monitoring [56]. A 2010 systematic review of 87 studies of behavior change strategies used in nutrition counseling demonstrated that MI was a highly effective counseling strategy [57].

Additionally, the nephrology literature has reported on applications of MI for kidney disease management. Fisher and colleagues [58] described efforts to improve fluid management among five hemodialysis adult patients. Their intervention combined MI with cognitive behavioral therapy for up to 12 sessions and found that three of the five patients reduced both the mean interdialytic weight gain and the frequency in which they gained more than 3% of their dry weight. van Vilsteren et al. [59] randomly assigned 96 sedentary hemodialysis patients to a low-to-moderate 12-week renal rehabilitation exercise program with or without the addition of four MI sessions to improve exercise adherence. They showed that relative to the control condition, the addition of MI yielded significant increases in reaction time, lower extremity muscle strength, increased exercise resulting in improved Kt/V, and three quality-of-life components.

MI can be utilized by the clinical team, especially MI-trained nurses, to help empower patients to be engaged in the self-management of their care [60,61]. A randomized trial of 793 patients with kidney disease in nine Dutch hospitals examined the use of an MI-trained nurse in coaching patients with kidney disease around adherence with self-management [62]. They looked at cardiovascular morbidity and mortality, all-cause mortality, renal function, vascular damage markers, and quality of life over the course of 5 years and found that supplementing care with an MI intervention slowed renal death and improved glomerular filtration rate outcomes. Cardiovascular outcomes, however, were not improved, which suggests a differential benefit related to kidney functioning.

MI has also been studied as it relates to adherence in managing kidney disease. A 2011 study examined the use of staff-delivered MI in an outpatient hemodialysis setting. They found improvements in dialysis attendance (less skipped visits) and length of treatment sessions (fewer prematurely shortened sessions), in addition to improved biomarker outcomes (i.e., phosphorous and albumin) [63]. In a 2014 study in Spain, six monthly treatment sessions which included both MI and cognitive behavioral skill training focused on self-management of CKD resulted in higher self-reported levels of treatment adherence, reductions in depression and anxiety, increased health-related quality of life, and improvement in biomarkers (albumin, hemoglobin, potassium, and phosphate) [64].

Innovative ways for utilizing MI in clinical practice are also being trialed within CKD clinical settings. In a feasibility study conducted at a rural medical center, investigators working with patients who had stages 1−3a CKD paired dietary logging via smartphone with weekly telephone-based MI sessions delivered by registered dietitians over 8 weeks [65]. Results of this small study were promising, with 88% of the sample recording dietary data on at least 75% of the days. Patients also reported high levels of satisfaction with the intervention, and improvements were found in overall sodium intake, weight, and daytime systolic and diastolic blood pressure. This study, along with other published work on the use of MI in the context of healthcare, demonstrates the versatility of MI in that it can be employed by a variety of health-care professionals and in various formats (face-to-face, telephone).

Future research directions in kidney disease management

Despite these applications of MI in kidney disease management, there are still additional areas to be explored. It is unclear if the beneficial impact of MI on CKD outcomes changes when morbidity with other chronic diseases (other than diabetes) is present. While it may be assumed that chronic disease profiles that have similarities in behavioral self-management (e.g., nutrition and physical activity requirement, medication adherence, and tracking) would also improve, the impact of MI on other co-occurring conditions like chronic pain, depression, anxiety, and cancer is less clear. It is possible that the mechanisms that significantly contribute to the effectiveness of MI (i.e., change talk) may not be the same mechanisms when working with patients with complex medical histories. Furthermore, given the higher incidence and prevalence rates of end-stage renal disease among non-Whites within the United States and the United Kingdom, further research to identify ways of utilizing MI to mitigate the progression of CKD among these populations is warranted.

Additionally, current literature focuses on MI-training at the nursing level likely due to the frequency of contact that nurses have with patients undergoing CKD treatments. Future work in kidney disease should focus on MI training at the physician, dietitian, pharmacist, and caregiver level. This expansion in training complements the increased focus on patient-centered care that is embodied in the spirit of MI. Additionally, MI training can empower members on the treatment team by offering them tools to support patients in navigating the complexities in CKD management. It is possible that the positive impact of MI on disease outcomes can be further actualized by having a full clinical and family/caregiver team to affirm self-management skills and reinforce change talk.

Another area of potential research is the use of MI to delay CKD disease onset (e.g., patients at risk for CKD with comorbid diabetes mellitus type 2), or delay the progression of disease (e.g., predialysis or transplant). In doing so, longitudinal studies could examine how different elements of MI can serve as a preventative tool (vs an interventional tool) and whether behavior changes are sustained over time.

Learning motivational interviewing

The complexity of treatment regimens has remained unchanged, and as such, the need for providers to be trained in effective strategies to engage patients in chronic disease management remains. Providers must be trained to understand how patients process all the information provided to them, and on what basis they make decisions about how to act in response to that information so that an effective collaboration is established. There has been increasingly more research examining the relative contribution of person-centered care to the effectiveness of MI [66], as well as other counseling modalities (including illness-integration, and guided self-determination) [67].

Literature on how to train providers in MI is well established. The most popular approach has been the use of several day workshops. Research on the effectiveness of MI workshops (expert-facilitated didactics and skill-building activities delivered in a group format) shows providers consistently improve their attitudes, knowledge, and confidence in MI, but immediate skill gains resulting from the training diminish within a few months [68−70].

A recent meta-analysis of MI training studies showed that the addition of approximately monthly post-workshop supervisory feedback and coaching sessions over a 6-month period was sufficient to sustain workshop training effects, with an overall MI skills training effect size of 75 [68]. Others have found that coaching MI-trained clinicians on their skills throughout the intervention results in greater beneficial effects, especially with medication adherence [71].

Several provider performance rating scales are now available that can be used to reliably supervise MI practice in this manner [72−75]. This approach to supervision is particularly important given that providers typically evaluate their performance more positively than when the same sessions are reviewed by their supervisors or independent judges [76]. Moreover, in the absence of supervision in MI, providers may be more prone to initiate informal discussions (i.e., chat) about matters that are unrelated to their patients' treatment [76–78].

Even with supervision, providers will vary in their capacity to learn MI. For example, Miller has speculated that a minimum level of pre-training empathic abilities might be necessary for providers to learn MI [79]. In addition, learning MI may require that providers sequentially build their skills in different stages. Miller and Moyers proposed eight stages (see Table 47.2) for learning MI [80]. First, providers need to develop openness to the spirit of MI such that they grasp the overriding philosophy of the approach (stage 1). Next, they must master the patient-centered counseling skills embodied in the OARS (stage 2), the foundation from which they then learn how to recognize and reinforce change talk (stage 3). Providers then learn strategies for evoking change talk (stage 4), dancing with discord (stage 5), and developing a change plan (stage 6). Training in consolidating and strengthening commitment comes next (stage 7). If MI is to be used with other treatment approaches, learning how to switch between the methods or integrate MI into other practices is the last stage (stage 8). Providers may vary in the sequence and degree to which they learn the skills embedded within each stage. Nonetheless, the stages of learning MI imply a training progression that might be used to organize the design of training programs. Moreover, they suggest that MI involves a complex set of skills that providers must use flexibly and adaptively in response to what patients say during their health-care appointments.

TABLE 47.2 Eight stages of learning motivational interviewing (MI) [80].

Stage	Definition
1	Developing an openness to interacting with patients with a spirit of collaboration, respect for autonomy, assumption of motives for change, and compassion
2	Developing proficiency in the use of patient-centered counseling skills such as open questions, affirmations, reflections, and summary statements
3	Recognizing and differentially reinforcing change talk as it naturally occurs in conversation and in the context of a patient's ambivalence
4	Eliciting and strengthening change talk in a goal-oriented fashion using a variety of techniques
5	Rolling with resistance using various strategies to avoid provoking arguments
6	Developing a change plan once a patient has made a clear commitment to change
7	Consolidating commitment to the patient's specific change plan
8	Switching between MI and other counseling methods as one moves beyond MI or returns to it when motivation wanes

A variety of training resources exist to learn MI. These resources include textbooks, treatment manuals, training videotapes, a supervision toolkit, and an international training group called the MI Network of Trainers (MINT). Many of these resources are accessible at www.motivationinterview.org.

Dissemination of motivational interviewing

MI has become very popular in the United States and internationally. Single State Authorities throughout the United States and their equivalent bodies in other countries frequently recommend MI as an empirically supported clinical approach they want providers to learn [58–61]. The MINT has garnered international appeal, with the training of new trainers occurring internationally each year. It may be that the person-centeredness of the approach and, hence, sensitivity to diverse cultural perspectives make MI broadly attractive among various cultural backgrounds [81]. Moreover, the number of publications about MI has increased exponentially in the past three decades as well as funded research grants examining applications of MI to a variety of clinical problems and populations.

Conclusion

MI is a recognized evidence-based practice for addressing behavioral problems that holds great promise for motivating patients with kidney disease to adhere to various aspects of the complex treatment regimens and other healthy lifestyle activities that are important for these patients. MI has a clear set of principles and strategies that guide implementation and substantial training resources to prepare providers to conduct MI proficiently. The popularity of MI continues to grow and the health-care field remains challenged to study if and how it works within its new applications, such as for the management of kidney disease, and to ensure that providers implement it with integrity to improve treatment outcomes. The nephrology community should learn how to apply MI techniques in CKD clinics and dialysis facilities. Carefully done studies will then need to be done to document the impact of MI on a variety of patient outcomes.

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CHAPTER

48

Anorexia and appetite stimulants in chronic kidney disease

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General considerations

Diminished appetite in patients with chronic kidney disease (CKD) is an important contributor to inadequate nutrient intake that leads, together with other concurrent risk factors, to the uremic protein-energy wasting (PEW) syndrome. Anorexia, nevertheless, is a complex term that involves not only metabolic signals but also anomalies in the system organs involved in nutrient intake as well as psychological and acquired aspects. Before discussing the intricacies of anorexia in CKD, we will briefly review the normal regulation of the feeding—hunger cycle.

Normal regulation of the feeding—hunger cycle

The regulation of appetite involves a heterogeneous feedback system that requires the participation of signals from the gastrointestinal tract, liver, circulating nutrients, fat stores, interleukins (ILs), and metabolizing cell products, all of which are integrated in the hypothalamus, inducing hunger or satiety [1—4] (Fig. 48.1). In a simplified way the hunger—satiety cycle starts in with the desire to eat, induced among others by ghrelin secretion. When the meal reaches the stomach, stimulates satiety signals: meal volume and composition induce distention and stimulate baroreceptors, cholecystokinin (CCK) release by duodenal cells, and peptide YY (PYY) release by ileum/colon cells, all of which inhibit gastric motility. These signals induce in addition central satiety via the vagus nerve. At a next step, satiety is further induced by circulating nutrients and metabolic end products, which regulate appetite by inducing gastrointestinal and liver peptide release (CCK, glucagon, and insulin). The gut-secreted incretins glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide, which activate glucose and insulin, release and increase intracellular ATP concentration, which again stimulates the vagus nerve and inhibits appetite.

Within the central nervous system (CNS), the melanocortin pathway located in the arcuate nucleus of the hypothalamus is a principal nexus through which nutritional cues converge and signal to influence food intake and energy balance. Two important pathways are induced at this level, the melanocortin receptor-4 (MCR-4) and proopiomelanocortin (POMC) pathways. Under normal conditions the activity of MCR-4 is increased by the suppression of orexigen hormones such as neuropeptide Y (NPY) and agouti-related protein (AGRP)-like activation of POMC-expressing neurons to produce α-melanocyte-stimulating hormone. This directly stimulates melanocortin-4 receptor (MC4-R), causing increased energy expenditure and reduced food intake.

POMC and AGRP neurons, and the induction of the MC4-R pathway represent the essence of the hunger—satiety cycle. They are responsive to nutritional signals, including adipose (such as adipokines and cytokines), stomach, gut (such as ghrelin, PYY_{3-36}, CCK, GLP-1) and pancreatic hormones (insulin, amylin), brain-derived energy balance—associated neurotransmitters and neuropeptides (such as catecholamines, GABA, serotonin, and NPY), dietary nutrients, and probably yet uncharacterized molecules [5,6].

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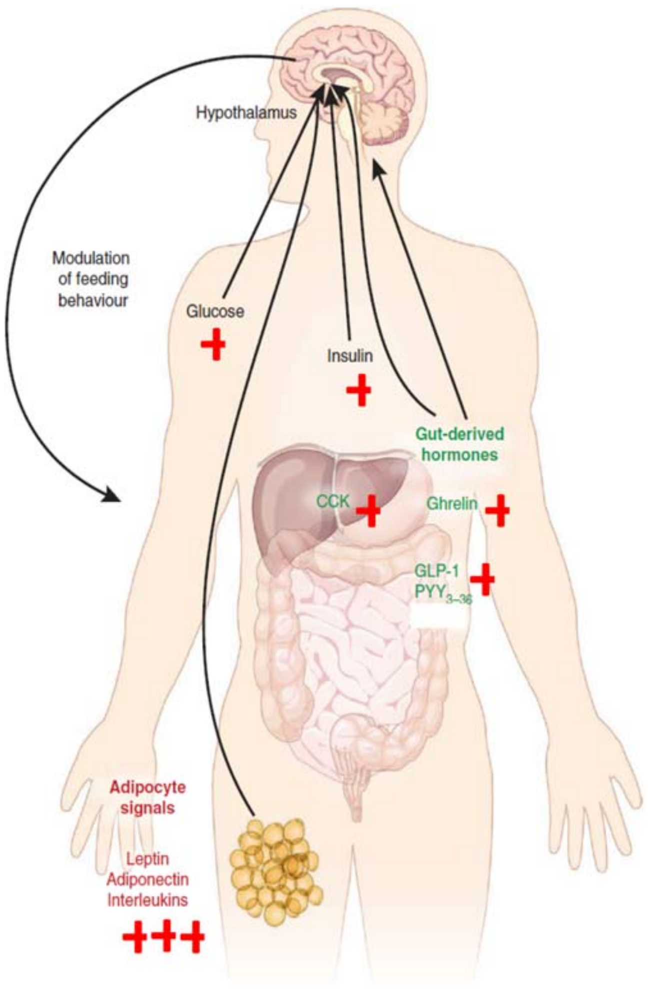


FIGURE 48.1 Gut-, liver-, and adipocyte-derived hormones, reflecting short- and long-term nutritional status, respectively, circulate in the periphery and signal to specific receptors in the brain. In the context of end-stage renal disease, there is evidence suggesting that the majority of these mediators are increased in circulation, either by simple retention or hyperproduction. *CCK*, cholecystokinin; *GLP-1*, glucagon-like peptide-1; *PYY3−36*, peptide YY residues 3−36. *Source: Modified from Yeo GS, Heisler LK. Unraveling the brain regulation of appetite: lessons from genetics. Nat Neurosci 2012;15(10):1343−9.*

To complete these biochemical pathways and illustrate the complexity of appetite regulation, the timing and amount of the next eating episode is not only dependent on internal factors, but to a large extent is also determined by external (conditioned) environmental and cultural (i.e., habits and traditions) cues. Humans eat not only to satisfy their appetite but also for many other reasons, for example, sensory hedonics, sensory stimulation, social pressure, mood, and boredom [1−3]. Last, but not least, problems in dentition, palatability, olfactory function, gastrointestinal tract, etc. are likely to influence both the willingness and choice of food as well. Thus anorexia is hard to quantify and also treatment of anorexia is complex and must involve a global multifaceted approach.

Methods of appetite assessment in studies involving patients with chronic kidney disease

Appetite can be measured in two ways. First, it can be measured with the help of subjective ratings. When used appropriately, subjective ratings have been shown to be reproducible, sensitive to exposures of food components, and predictive of food intake. However, it should be noted that appetite may not always be accessible to patient introspection and that people do not always eat when they are hungry and do not always refrain when satiated. Second, appetite can be measured by actual food intake. The degree to which food intake reflects appetite is nevertheless debatable, as there are many factors that may intervene: cognitive factors such as dietary restraint and external factors such as availability, hedonic properties of food, and social circumstances.

Research methodology on anorexia usually includes rating scales to assess appetite, such as the visual analog scale (VAS) [7,8]. More inaccurate, but perhaps easily implementable in the clinical setting, is the use of self-reports of the patient's appetite [9−12], which have shown to validly correlate with both dietary energy and protein intake [10]. The simplicity of this question is as follows: "How would you grade your appetite in the last week?" adhered to a 4-point scale: (1) good, (2) sometimes bad, (3) often bad, and (4) always bad [9].

Prevalence of anorexia and clinical implications in patients with chronic kidney disease

Anorexia is a common finding in CKD patients which typically develops when glomerular filtration rate is less than 10%−25% of normal and increases in severity with the progression toward end-stage renal disease (ESRD) [13]. While the prevalence of this condition in early CKD stages is, to our knowledge, unknown, it is reported in generally 35%−50% of the patients on dialysis [14] as shown in contemporary studies (Fig. 48.2), with a higher proportion of self-reported poor appetite on dialysis-treatment days [15]. The consequences of anorexia in this setting are important and should not be underestimated. Four medium−large sample size studies consistently show that a worsening in appetite progressively associates with increased mortality risk [8−10,12] (Fig. 48.3). Opposing to this, a subsequent recent study did not observe this mortality association in incident dialysis patients [16], but self-reports of appetite during the first days of dialysis initiation may be influenced by the

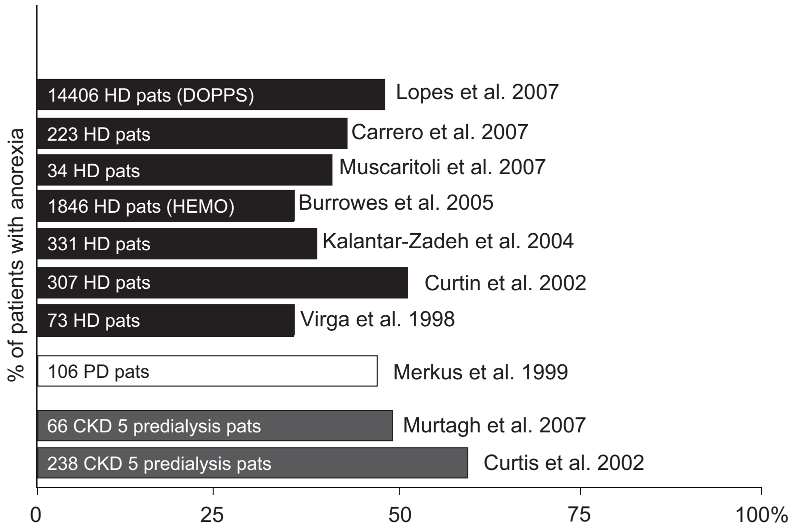
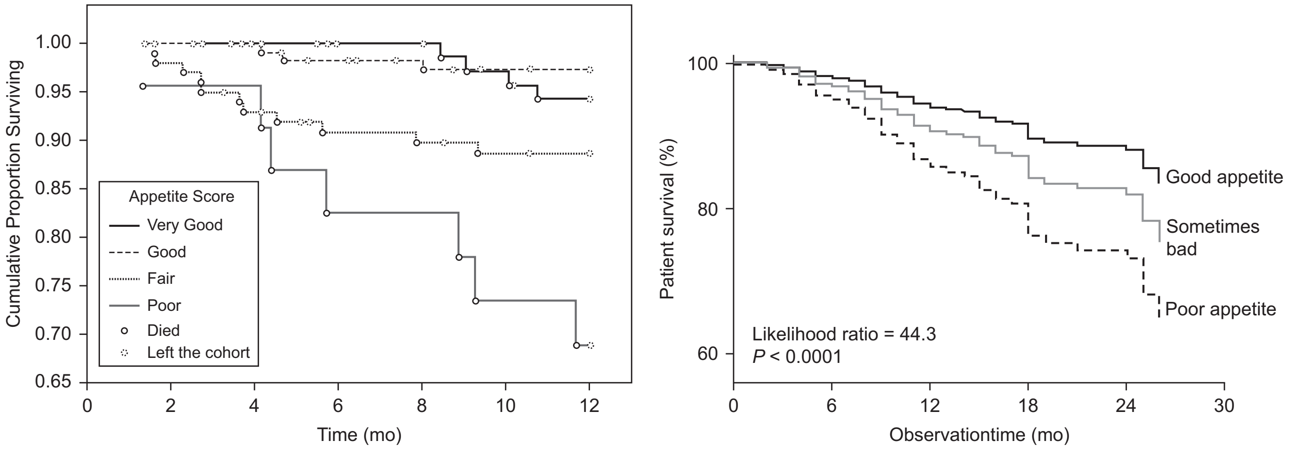


FIGURE 48.2 Reported prevalence of diminished appetite in ESRD, PD, and HD patients from various cohort studies. *ESRD*, End-stage renal disease; *HD*, hemodialysis; *PD*, peritoneal dialysis.



Kalantar-Zadeh et al. Am J Clin Nutr 2004; 80(2):299-307.

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FIGURE 48.3 Kaplan–Meier survival curves from two studies showing the impact that a single self-report on patient's appetite has on the prediction of 1-year and 2-year mortality. Both studies included prevalent patients undergoing hemodialysis. *Source: Reproduced with permission from Carrero JJ, et al. Comparison of nutritional and inflammatory markers in dialysis patients with reduced appetite. Am J Clin Nutr 2007; 85(3):695–701; Kalantar-Zadeh K, et al. Appetite and inflammation, nutrition, anemia, and clinical outcome in hemodialysis patients. Am J Clin Nutr 2004;80(2):299–307.*

overwhelming experience that the patients are being exposed to. In addition, anorexia increases hospitalization rates by up to 22%, with the costs that this implies for healthcare [10,12,17]. Finally, anorexia is perceived by dialysis patients as a significant worsening in their quality of life [8,11]. Ultimately, anorexia results in diminished and inadequate nutrient intake, resulting in important macro- and micronutrient deficiencies that contribute to the PEW syndrome [18].

Pathogenesis of anorexia in chronic kidney disease

A spontaneous decrease in dietary protein intake and appetite occurs with progressive reduction in renal function [19,20]. Traditionally, diminished appetite has been considered a sign of uremic intoxication [21]. However, anorexia cannot be confined only to appetite regulators, as it links to several other important complications of CKD that need to be put in

TABLE 48.1 Summary of potential mechanisms contributing to diminished appetite and undernutrition in chronic kidney disease (CKD) patients.

Causes of anorexia in CKD	Comment
Disrupted molecular signaling	
Altered CCK, PYY, ghrelin	Satiety arises earlier in dialysis patients during meal consumption. Ghrelin administration may have potential as therapy
Cytokine and adipokine retention	By both central and peripheral mechanisms. Potential as therapy through antagonism of the melanocortin-4 receptor
Low branched-chain amino acids	Leading to increased serotonin (appetite suppressant) production. Potential as therapy by oral supplementation
Factors inherent to the dialysis procedure	
Glucose absorption in dialysate	Feeling of fullness, inhibition of appetite by glucose degradation products, delayed gastric emptying by dialysate exchange
Retention of uremic suppressants/toxins	Unknown molecules of middle size
Alterations in the organs involved in nutrient intake	
Oral manifestations: taste abnormalities, dry mouth, tongue coating, mucosal inflammation, or oral ulceration	Problems with swallowing and food perception. Possibilities for treatment
Tooth problems: missing/decayed teeth, periodontitis	Problems with chewing, patient may avoid high-fiber foods. Possibilities for treatment
Impaired olfactory function	Affects taste and food perception. Related to systemic inflammation and malnutrition in CKD
Functional gastrointestinal disturbances: gastric distension, constipation, motility disorders, and impaired gastric emptying, diabetic gastroparesis	Will influence patients in their choice of food items that may associate with painful digestion/evacuation. Possibilities for treatment
Infections in the gastrointestinal tract	Possibly contributing also to systemic inflammation. Possibilities for treatment
Social, psychosocial causes	
Depression and anxiety, attitude toward disease	
Poor physical activity	
Loneliness and limited ability to do daily living (cooking, buying groceries, etc.)	
Economical limitations	
Poor nutritional knowledge on available food choices	

CCK, Cholecystokinin; *PYY*, peptide YY.

context. A correct understanding of the multifactorial causes of uremic anorexia is necessary to appropriately tackle this problem. Multiple causes of diminished appetite in the uremic population are discussed later and summarized in Table 48.1.

Retention of uremic toxins

Earlier animal and human studies identified retention of uremic toxins as a determinant of anorexia in ESRD [19,20]. Anderstam et al. [22] showed that rats given an intraperitoneal injection of plasma ultrafiltrate from uremic patients decreased food intake, as opposed to rats injected with plasma ultrafiltrate from healthy volunteers (Fig. 48.4). After the initiation of maintenance dialysis, food intake and nutritional markers usually improve, although not fully, indicating that dialysis removes certain anorectic toxins, but not all. Similarly, it can be hypothesized that the accumulation of these appetite suppressors may reach its maximum peak before each hemodialysis (HD) treatment, and indeed food intake is lower during HD days [15].

Dialysis patients show *slower eating* and *increased feeling of fullness* before the meals as compared to non-CKD patients [23] (Fig. 48.5). Early satiety and slow gastric emptying in dialysis patients have been linked to the dysregulation of short-term appetite modulators from the *gastrointestinal* tract, all of which seem elevated in ESRD patients likely because of uremic toxin retention. CCK levels were increased as compared to control individuals and associated with fullness and hunger perception in peritoneal dialysis (PD) patients [24]. PYY levels were also significantly elevated versus control individuals in HD patients [25], and meal provocation studies disclosed a marked dysregulation of PYY during the postprandial secretion in these patients [26], leading to earlier satiety and lower food intake than their age- and sex-matched controls.

Ghrelin is a gut orexigenic peptide that increases appetite and adjusts both short- and long-term energy balance through the expression of orexigenic neuropeptides and increased growth hormone release. A more in-depth review on the biology of ghrelin and its complex associations with various pathophysiological pathways of uremia is suggested here [27]. Ghrelin levels are elevated in dialysis patients presumably due to retention [28]. However, postprandial ghrelin regulation in dialysis patients does not differ from that of controls [29]. Given that ghrelin increases appetite, the elevated levels found in ESRD patients have been interpreted as a sign of resistance to the action of ghrelin. However, it is likely that other concurrent conditions, such as preexisting PEW, may have masked and confounded these observations in cross-sectional

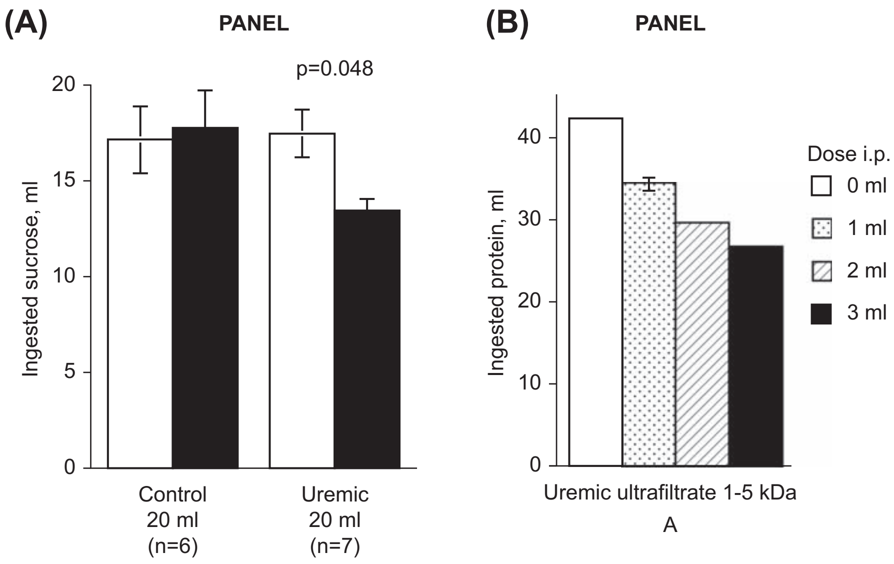

FIGURE 48.4 Anorexia as a sign of uremic intoxication. Rats given an i.p. injection of plasma ultrafiltrate from uremic patients with decreased food intake, as opposed to rats injected with plasma ultrafiltrate from healthy volunteers (A). This inhibition of food intake seemed to be dose-dependent (B). *i.p.*, Intraperitoneal. *Source: Reproduced with permission from Anderstam B, et al. Middle-sized molecule fractions isolated from uremic ultrafiltrate and normal urine inhibit ingestive behavior in the rat. J Am Soc Nephrol 1996;7(11):2453–60.*

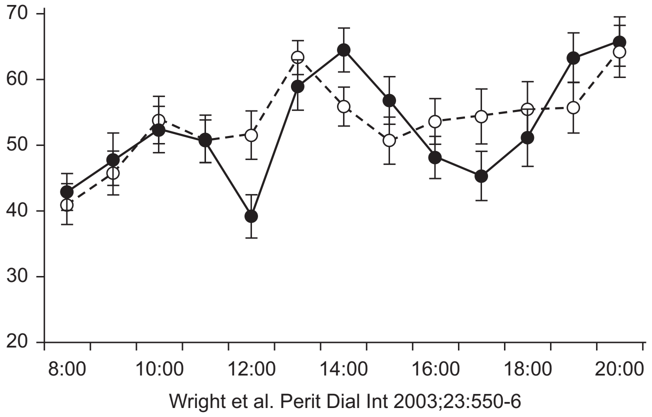

FIGURE 48.5 Mean fullness scores at hourly time points for healthy controls (*closed diamonds*) and patients undergoing peritoneal dialysis (*open circles*) during a full day. While fullness and satiety peaks in healthy controls are marked by each episode meal (i.e., breakfast, lunch, and dinner), such peaks are much flattened in peritoneal dialysis patients, meaning that they have a general feeling of fullness along the day and a weaker eating drive. Statistically significant differences ($P < .05$) by means of *t*-tests were observed in the change in fullness rating at lunchtime. *Source: Reproduced with permission from Wright M, et al. Disturbed appetite patterns and nutrient intake in peritoneal dialysis patients. Perit Dial Int 2003;23(6):550–6.*

analyses [30]. Ghrelin circulates in plasma in two major forms: acyl ghrelin, which promotes food intake, and the abundant desacyl ghrelin (>90%), which on the contrary may induce a negative energy balance by decreasing appetite and delay gastric emptying [31]. Consequently, desacyl ghrelin levels have been found elevated in anorectic HD patients as compared to nonanorectic ones [32]. Interestingly, the acyl-ghrelin form was reported lower in HD patients and did not exhibit the premeal spike as observed in healthy controls [25].

Of the long-term regulators of appetite, hyperleptinemia ensues in advanced CKD due to decreased renal clearance [33]. *Leptin* is produced by adipocytes and provides information on the availability of body fat stores to the hypothalamus. A detailed discussion of leptin’s biology and implication in CKD is given elsewhere [34,35]. Although *leptin* appears as an important central mediator of anorexia in animal models [36], human data on leptin in relation to uremic anorexia and PEW are so far inconclusive. Hyperleptinemia does not seem to be associated with worse appetite or worse nutritional status in dialysis patients [37–39]. It has been proposed that because anorectic patients are subjected to increased loss of body fat, leptin will primarily reflect fat stores in the catabolic uremic milieu and obscure any real link to eating behavior [40,41]. Although elevated leptin levels may be a consequence of other concurrent risk factors and share links with systemic inflammation [33], antagonizing leptin receptors at the hypothalamus may represent a future therapeutic target as discussed later. *Visfatin* is not only an adipokine but also an intracellular protein upregulated in times of low-nutrient availability, which gets activated to promote cell survival during starvation [42]. Visfatin concentrations have been found in human cerebrospinal fluid (CSF) and are linked to both appetite and body weight regulation [43]. In ESRD patients the reported hypervisfatinemia [44] may be a counterregulatory response to central visfatin resistance, because elevated (instead of reduced) visfatin levels were associated with anorexia and low fasting serum amino acids (AAs), glucose, and blood lipids, altogether indicating reduced plasma nutrient availability [45]. For both the cases of visfatin and leptin, conditions typical of advanced CKD can cause the inhibition of brain-to-blood transport, leading to the accumulation of endogenous metabolites and drugs in the brain [46]. It is possible that central action of these and other orexigens may be hampered by uremic toxicity.

Imbalances in serum AA profile may contribute to a "brain hyperserotoninergic-like syndrome" that favors anorexia in ESRD. The altered AA pattern in CKD includes reduced essential/nonessential AAs ratio and lower branched-chain AAs [47], which would theoretically favor high levels of free tryptophan in the CSF. Tryptophan is the precursor of serotonin, a mediator of appetite suppression. In addition, the nitric oxide (NO) system is altered in CKD, with the accumulation of NO synthase inhibitors that interfere with tryptophan metabolism and enhance serotonin production [21]. While this hypothesis has not been confirmed in CKD [47], the fact that oral branched-chain AA supplementation improved energy intake and nutritional status in a small placebo-controlled double-blind study of malnourished dialysis patients [48] may indicate its potential beneficial role.

Some appetite-related nervous system—derived hormones also seem to be altered in advanced CKD. Increased NPY levels along with a lack of circadian variation [25] have been reported in HD patients [25,49]. Norepinephrine levels have been reported elevated in HD patients but did not exhibit the normal nocturnal dip either [25]. Finally, it has been proposed that the commonly observed suppressed parasympathetic activity in CKD patients may contribute to anorexia [25]. Interestingly, a recent animal study observed marked neurodegeneration in the anorectic anx/anx mouse accompanied by the generation of reactive oxygen species (ROS) and subsequent dysfunction in the mitochondrial oxidative phosphorylation system [50]. It is interesting to speculate that ROS in advanced CKD may parallel some of these observations as also encountered in human anorexia nervosa.

Alteration in the organs involved in nutrient intake

A number of abnormalities commonly present in CKD may indirectly affect and/or mask the feeling of hunger in ESRD patients, likely influencing and limiting dietary intake. The enjoyment of food depends not only on its taste but also on its odor as it approaches the mouth and the release of volatile organic substances within the mouth. In addition, the temperature and texture of the food, as well as the masticatory sounds, all produce the ultimate sensory experience. All of these factors seem altered in ESRD such as taste abnormalities (palatability, acuity, and metal flavor), dry mouth, tongue coating, mucosal inflammation, or oral ulceration (that will altogether ultimately lead to swallowing problems), which can all contribute to inappetence. Taste loss is common in ESRD [51,52], and its strong association with kidney function suggests that the retention of uremic toxins may be responsible [51].

Typical *dental problems* such as decayed, missing, or filled teeth and the increased prevalence of periodontitis in the CKD population likewise create chewing and/or biting problems, making patients less likely to consume high-fiber foods such as bread, fruits, or vegetables and, therefore, risking their essential nutrient intake [14]. *Olfactory function* is also impaired in HD patients and related with the severity of PEW [53]. The recent observation that olfactory dysfunction in ESRD is readily reversible by the HD session [54] challenges, however, this hypothesis.

Loss of appetite in uremia is related to a number of common *gastrointestinal disturbances*, including gastroesophageal reflux, gastric distension, constipation, motility disorders, and impaired gastric emptying [55–57], all of which will create discomfort associated to nutrient digestion and subsequent food aversion. *Chronic diabetic gastroparesis* may be an important problem resulting in reduced nutrient intake. With prolonged diabetes the vagus nerve becomes damaged and develops autonomic neuropathy. This disturbance results in prolonged abdominal distension and exacerbated feeling of satiety. Other indirect causes of anorexia may relate to stomach irritation caused by medications, such as iron compounds or phosphate binders. Gastrointestinal infections are important and underappreciated contributors to anorexia in CKD. In the study by Aguilera et al. [58], *helicobacter pylori* infection in PD patients was associated with a poor nutritional status, increased systemic inflammation, and worse appetite scales. *Bowel bacterial overgrowth syndrome* was also associated with anorexia and inflammation in PD patients [59]. CKD in itself profoundly alters the intestinal barrier structure and the microbial flora [60,61]. The biological impact of these phenomena is largely unknown but it is possible that they may play a major role in the pathogenesis of inflammation and uremic toxicity [60], which may per se induce appetite loss. Recent studies also indicate that short-chained fatty acids produced by the microbiome can induce the release of GLP-1 from cells in the colon, which raises the possibility of an even greater influence of our microbiome with the body's energy metabolism and immune system [62].

Medications and dialysis

Drugs can affect food intake, and food intake can also affect the efficacy of some drugs. Most CNS stimulants lead to appetite loss, and certain antihypertensive drugs (captopril) may result in abnormalities in taste/smell of food. Drugs such as codeine and morphine can decrease peristalsis causing constipation. Drugs can also affect absorption, metabolism, and excretion of nutrients: NSAIDs can alter gastric acidity impacting on intestinal mucosa, and antibiotics can bind to some nutrients such as Fe, Mg, and Zn with ensuing difficulty in their absorption. Others, like corticosteroids, may actually increase appetite.

The dialysis procedure may further aggravate anorexia. Animal studies demonstrated that PD solutions with increasing glucose concentration gradually inhibit ingestive behavior [63] (Fig. 48.6). Generation of glucose degradation products (GDP) has been suggested as mediators of uremic anorexia, as heat sterilization of glucose PD solutions (thus increasing GDP production) inhibited intraoral intake in mice in a dose-dependent manner as compared to filter sterilization [64]. Although there is no strong evidence suggesting that PD patients have worse PEW compared to HD patients, it seems that PD patients are more often bothered by diminished appetite and gastric discomfort [21,65–67]. PD fluid exchange has been shown to delay gastric emptying and, thus, leads to fullness interfering [29,68]. Practically no studies have been performed investigating whether HD induces appetite loss, but the absence of evidence does not mean evidence of absence. HD patients often skip one meal in connection with their dialysis session [69].

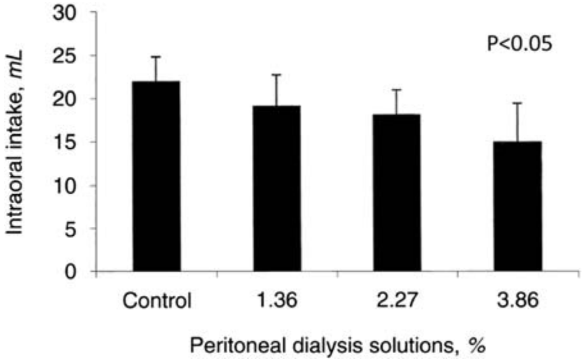

FIGURE 48.6 Peritoneal dialysis solutions with increasing glucose concentration gradually inhibited ingestive behavior in animal models with partial nephrectomy. *Source: Reproduced with permission from Zheng ZH, et al. Acute effects of peritoneal dialysis solutions on appetite in non-uremic rats. Kidney Int 2001;60(6):2392–8.*

Psychosocial factors and comorbidities

ESRD patients are a heterogeneous population where concomitant illness such as cancer, heart/vascular disease, or diabetes may contribute to the onset of anorexia. While some studies do not associate anorexia in uremia with comorbidities [9,11,16], an increased prevalence of diabetics across worsening appetite scores was reported in the Dialysis Outcomes and Practice Patterns Study [10]. Also, age and comorbidities were higher among anorectic HD patients from Italy [17]. Thus a last consideration is that CKD is eminently a disease of the elderly [63,64], and altogether it may be difficult to separate CKD-induced appetite loss from the diminished appetite and nutritional derangements that naturally develops with aging and disease.

Depression (Fig. 48.7) *and anxiety* will obviously influence the willingness to eat, and observational reports show that appetite is, in fact, poorer when patients score worse on their depression tests [12,70]. Common alterations in ESRD such as low thyroid hormone levels [71] may also influence food intake. Additional factors, more difficult to evaluate and to treat, that may promote low-nutrient intake are loneliness (living alone, widow or divorcee, and social isolation), limited ability to do activities of daily living (manage themselves, cook or buy groceries), or economic restraints. Lack of education on adequate dietary needs and CKD-specific dietary restrictions can result in poor dietary intake with an inadequate selection of food choices. Diseases that interfere with the ability of the person to eat or prepare food, for example, stroke, tremors, or arthritis, can also lead to decreased food intake.

Systemic inflammation

An increased loss of appetite is associated with elevations in biomarkers of systemic *inflammation* [9,11,72,73] (Fig. 48.8). Besides many other implications in the organism [74,75], proinflammatory cytokines are capable of inducing anorexia by both central and peripheral mechanisms. Central mechanisms are mediated by the direct effect of cytokines on hypothalamic neurons and/or the generation of mediators targeting brain target sites [21,76]. At a nuclear level, nuclear factor kappa B activation also suppresses food intake, at least in mice, by direct activation of the POMC promoter at the hypothalamus [77]. In addition, peripheral mechanisms have to do with the effect of inflammation on the ESRD-related complications that contribute to

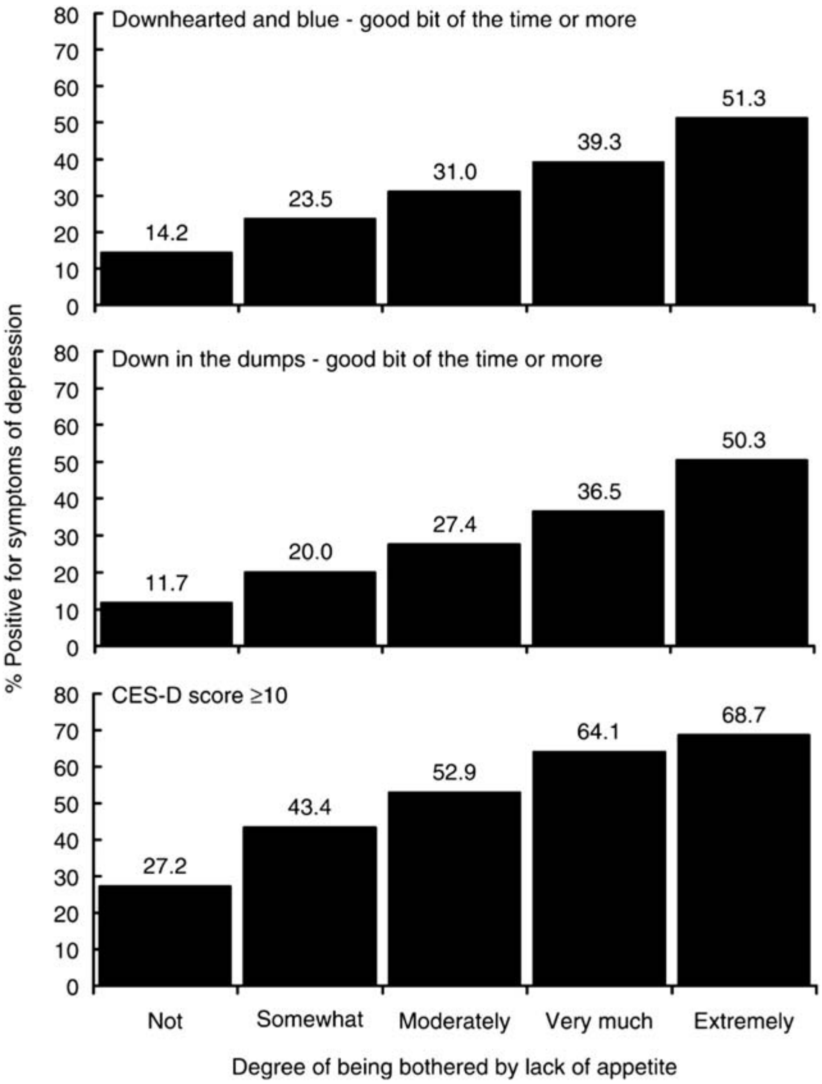

FIGURE 48.7 Lack of appetite is associated with signs of depression. This figure shows percentage of patients with higher levels of symptoms of depression by degree of being bothered by the lack of appetite. Downhearted and blue ($n = 14{,}008$); Down in the dumps ($n = 8623$); CES-D screening index score ($n = 6952$). *CES-D*, Center for Epidemiological Studies Depression. *Source: Reproduced with permission from Lopes AA, et al. Lack of appetite in haemodialysis patients—associations with patient characteristics, indicators of nutritional status and outcomes in the international DOPPS. Nephrol Dial Transplant 2007;22(12):3538–46.*

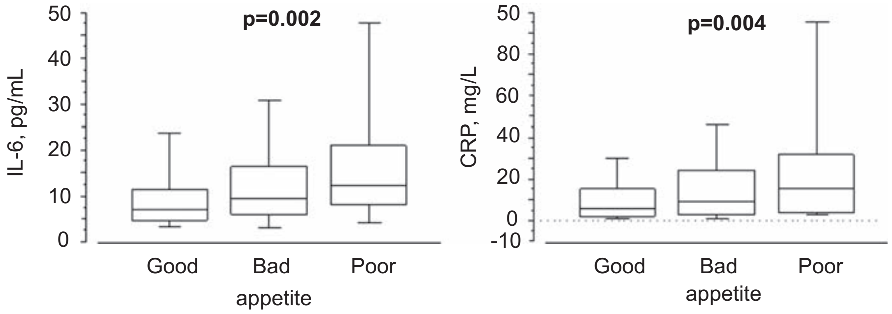

FIGURE 48.8 Markers of systemic inflammation increase across worsening appetite categories in a cohort of patients undergoing maintenance hemodialysis. *Source: Adapted from Carrero JJ, et al. Comparison of nutritional and inflammatory markers in dialysis patients with reduced appetite. Am J Clin Nutr 2007;85(3):695–701.*

anorexia [78]. For instance, in dialysis patients, depressive symptoms correlate to increased IL-6 levels [79]. Chronic inflammatory processes in the periodontium are associated with an elevation of inflammatory biomarkers in HD patients [80]. Impaired olfactory function associates with inflammation [53], and CRP directly blocks the effects of leptin upon satiety and weight reduction [81], suggesting a link between systemic inflammation, leptin resistance, and CKD. Alterations in the gastrointestinal tract, such as dyspepsia and nausea, were associated with increased inflammatory response biomarkers in dialysis patients [82]. IL-1 and TNF interfere with tryptophan and serotonin turnover [83]. TNF decreases NO levels and increases sympathetic activity [84], and low serum AAs are, in part, consequence of systemic inflammation [85]. Altogether, these interactions emphasize the importance of the interplay between inflammation and PEW and its role in exacerbating poor outcomes [86]. Accordingly, it can be speculated that systemic inflammation may constitute an integrative factor in the development and worsening of poor appetite in ESRD patients.

Treatment of anorexia in chronic kidney disease

The prodromal step for anorexia management is early identification. A simple inquire to the patient about his/her appetite in the last weeks may represent an alarm signal for further follow-up and assessment [9–12]. Such information is costless and can be done on a routine basis. Treatment of anorexia in ESRD is complex, and there are limited data for evidence-based approaches [87]. In Fig. 48.9, we propose several action points when treating anorexia in ESRD.

Identify and treat underlying causes

As a first step one should screen, identify, and if possible treat underlying causes of anorexia, including gastrointestinal infections and disorders, depression, poor oral and dental health, and the presence of periodontitis or diabetic gastroparesis. In the case of alterations in the GI tract, gastric motility agents, such as domperidone, metoclopramide or cisapride, and proton-pump inhibitors, may be used with caution and close monitoring. Two studies show the need for a more stringent screening and management of bacterial infections: general antibiotic treatment of *helicobacter pylori* infection and *bowel bacterial overgrowth syndrome* in PD patients yielded important improvements in appetite scores and resulted in reduced systemic inflammation [58,59].

A comprehensive nutritional, dietary, and appetite assessment to determine the presence or absence of PEW is recommended. A detailed personal interview with the patients may help us to detect other psychological or social situations that further enhance low food intake, such as problems related to self-feeding, access to food, and eventually, identification of active psychic, social, medical, dialytic, or medicine-related issues that could affect food intake. Of note, the treatment of depressed HD patients with fluoxetine resulted in improved systemic inflammation and increased food intake [88,89].

In the case of diabetic gastroparesis, several recommendations can be given, including (1) to eat small frequent meals, since high volumes can slow gastric emptying; (2) to consider mechanically altered foods (pureed, ground); (3) not to limit fat, which can provide additional calories; and (4) to stand up for at least 1–2 hours after eating. If oral dietary modifications are not effective, current approved treatment options include metoclopramide and gastric electrical stimulation. Antiemetics, domperidone, or erythromycin may also produce symptom relief [90].

Support and promote food intake and physical activity

Nutritional counseling to correct reduced or unhealthy nutrient intake should be given to all patients on a regular basis as a mean to promote food intake and improve the patient's knowledge on food options with respect to their disease. Promotion of physical exercise and salutary

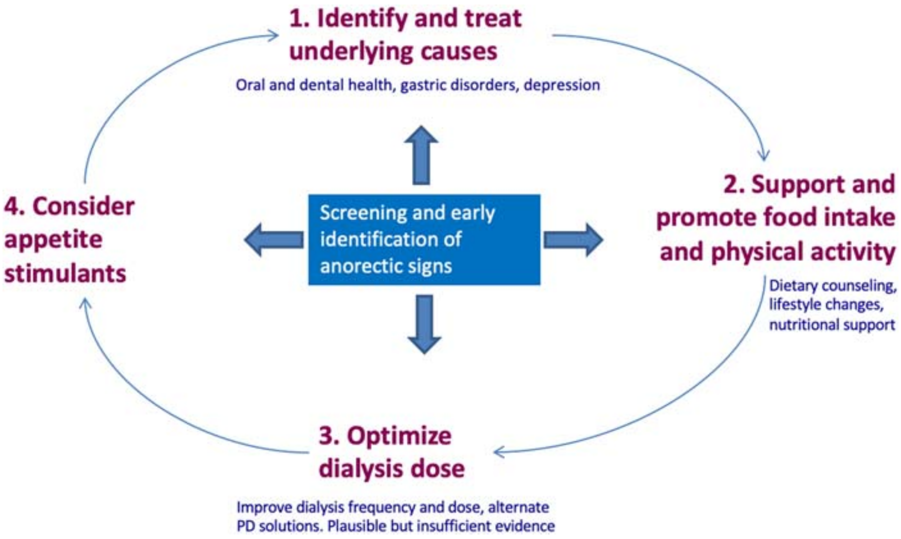
1. Identify and treat underlying causes
Oral and dental health, gastric disorders, depression
Screening and early identification of anorectic signs
2. Support and promote food intake and physical activity
Dietary counseling, lifestyle changes, nutritional support
3. Optimize dialysis dose
Improve dialysis frequency and dose, alternate PD solutions. Plausible but insufficient evidence
4. Consider appetite stimulants

FIGURE 48.9 Proposed action points to treat anorexia in patients with CKD. At all phases, ongoing and frequent monitoring is a requirement to sustain optimal outcomes and adapt course of action. *CKD*, Chronic kidney disease.

lifestyle modifications may indirectly impact on the patients' energy and calorie intake through both improved general well-being [91].

Nutritional support in the form of oral supplements, parenteral nutrition, or intradialytic parenteral nutrition is a valid alternative to ensure adequate nutrition, and perhaps also to improve appetite. Alluding to the "brain hyperserotoninergic-like syndrome" hypothesis earlier discussed, a randomized controlled crossover trial with 28 malnourished PD patients provided daily branched-chain AAs supplementation (12 g/d) for 6 months and resulted in improved nutritional status and increased spontaneous oral food intake versus placebo [48]. A more recent study also observed improvements in serum albumin and protein catabolic rate together with a decrease in CRP after the supplementation of oral AAs versus placebo [92]. Fish oil supplementation elicited meaningful trends toward improvements in subjective appetite in a noncontrolled study, including 28 HD patients from Australia [93], presumably via the antiinflammatory effects of $n-3$ fatty acids.

Providing supplements to anorectic patients may be a way to initiate the wheel of food intake. It has been argued, however, that intake of oral nutritional supplements (ONS) promotes fullness and the patient would, in turn, skip a meal. Boudville et al. [94] addressed this issue in a crossover trial of 13 PD patients. Patients were given a standard ONS or placebo 2 hours or 30 minutes before lunch. Lunch was provided as a self-select buffet-style meal, and food intake was recorded and measured. Results showed that patients felt hungrier after the placebo drink than after ONS. Patients reported feeling fuller and less able to eat than before, especially when consuming ONS 30 minutes before the lunch. However, this did not significantly nor clinically influence the amount of subsequent food calorie or protein intake [94]. Nevertheless, alternatives to prevent a possible impact on appetite feeling may be to advice consuming ONS after the meals or during the dialysis session, and/or advice using ONS throughout the day instead of water to ingest medication.

Optimize dialysis regimes

Optimizing dialysis regimes could potentially improve appetite in ESRD patients. Theoretically, increased dialysis adequacy may render not only an enhanced elimination of certain toxins and appetite suppressants, but also a general feeling of well-being, increased physical activity, fewer dietetic restrictions, and decreased dose of medications. The Hemodialysis (HEMO) Study showed that appetite scores were not differentially affected by increased dialysis dose or flux. Although the average decline in equilibrated protein catabolic rate during follow-up was significantly less in the high dose than the standard dose group, the differences were subtle and neither intervention prevented deterioration in nutritional status over time [95]. It has been, therefore, suggested that dialysis frequency rather than dialysis dose may be more important in the improvement of nutritional status [96]. In fact, a number of small uncontrolled studies suggest that the increase in dialysis frequency through short daily HD or nocturnal HD may improve nutritional status, appetite, and food intake [97–100]. Molina et al. [101] randomized 33 adults with CKD Stage 5 undergoing maintenance high-flux HD to either postdilution online hemodiafiltration or to remain on high-flux HD for 12 months. Results showed that hemodiafiltration, compared with high-flux HD, preserved muscle mass, increased appetite (VAS scale) and protein intake, and reduced the inflammatory state related to uremia and dialysis, supporting the hypothesis that high convection volume can benefit nutritional status and prevent PEW in HD patients.

In PD, one study reported an improvement in appetite scales through applying increased daily dialysate volume [102]. Davies et al. [103] performed an open, prospective, "intention to treat" study in which malnourished (according to subjective global assessment) long-term anuric PD patients received an intended dialysis dose increase of 25% and were reassessed after 6 months. Dialysis dose was not increased in the remaining nonmalnourished patients, unless dictated by uremic symptoms. In this setting, increased dialysis dose increased dialysis-derived calories, stabilized body weight, and improved creatinine appearance. Oral calorie intake improved, as did plasma albumin after an initial decline. There was, however, no increase in protein intake, as judged by either dietetic interviews or protein nitrogen appearance. These modest effects on nutritional status were not supported by the results from the Adequacy of PD in Mexico study, in which albumin levels or nitrogen protein appearance did not improve after increased peritoneal clearance [104]. Alternation with nonglucose-based solutions has also been associated with increased nutrient intake and more anorexigenic profile in both animal studies and a recent randomized trial [64,105,106].

Use of appetite stimulants

The use of appetite stimulants should be considered in anorectic ESRD patients where previous suggested steps have failed. Various pharmacologic agents are available in the market, but megestrol acetate is the only one for which there are clinical studies in ESRD patients. Megestrol acetate is a synthetic hormone (progestogen) effects of which on appetite stimulation have mainly been studied on cancer cachexia. Table 48.2 summarizes available studies and main results with megestrol acetate in ESRD. All studies, including two randomized controlled trials, report improvements in appetite and dietary intake, weight gain, and serum albumin [107–114]. A limitation of these studies is their relatively small sample size. Although in principle megestrol acetate could be a valid option for treating anorexia in ESRD, caution is needed in the close monitoring and follow-up of patients for possible side effects. A few of these studies report cases of diarrhea, overhydration, hyperglycemia, ACTH secretion [113,114], and Cushingoid features in children [112].

Besides its orexigenic actions, ghrelin may favorably influence other pathways such as inflammation, vascular resistance, cardiac output, or growth hormone [115]. It is presently being considered a therapeutic agent in diseases such as cancer cachexia, chronic heart failure, or arthritis [115]. Available studies to date show beneficial effects but are limited in general by a reduced sample size and short duration. Initial evidence in dialysis patients suggests that subcutaneous acyl-ghrelin administration improves short-term (single dose and 1-week treatment) energy intake and energy balance in patients with mild-to-moderate malnutrition [116,117]. These results, although promising, should be interpreted with caution until further research evaluates the safety and tolerance of long-term ghrelin administration in dialysis patients [118].

Central effects of both adipokines and cytokines on anorexia are mediated by the hypothalamic MC4-R system. Both the activated macrophage and the activated adipocyte secrete these molecules to plasma and, via the vagus afferent nerve, activate the melanocortin receptor system altering the balance food intake/energy expenditure. Pharmacologic manipulation has shown that agonizing the MC4-R causes weight loss and antagonizing the MC4-R produces weight gain. Interestingly, Cheung et al. [119] reported that intraperitoneal administration of MC4-R antagonists stimulated food intake and weight gain in uremic mice. Most interesting in this study is the secondary observation that neuropeptide signaling pathways also affected expression of key proteins involved in muscle mass maintenance [119], linking uremic anorexia, and muscle catabolism by common pathways. Multiple classes of MC4-R antagonists have been reported and

TABLE 48.2 Summary of reported studies using megestrol acetate as a mean to improve anorexia and nutritional status in patients with chronic kidney disease.

Reference	Number of patients (dialysis modality)	Dose	Study design	Outcomes
Boccanfuso et al. [107]	17 (HD)	400 mg/d for 6 months	Prospective observational	↑Appetite and weight
Costero et al. [108]	32 (PD)	160 mg/d for 6 months	Uncontrolled	↑Appetite and weight
Rammohan et al. [109]	10 (HD)	400 mg/d for 4 months	Uncontrolled	↑Weight, albumin, energy intake, and quality of life
Monfared et al. [110]	22 (HD) hypoalbuminemic	80 mg/d for 2 months	Randomized controlled	↑Albumin and protein catabolic rate
Yeh et al. [111]	9 (HD) wasted male patients	800/d for 5 months	Randomized controlled	↑Weight (both fat and fat-free mass) and exercise capacity. ↑Appetite and well-being (trends)
Hobbs et al. [112]	25 pediatric CKD patients	Tapered doses 14.4 mg/kg/d for 5.4 months	Retrospective observational	↑Weight. *Side effects:* Cushingoid features ($n = 1$)
Golebiewska et al. [113]	12 (HD) hypoalbuminemic	160 mg/d for 6 months	Uncontrolled	↑Weight, albumin, subjective global assessment. *Side effects:* overhydration, excessive weight gain, and hyperglycemia
Fernández Lucas et al. [114]	16 (HD)	160 mg/d for 3 months	Uncontrolled	↑Weight, albumin, creatinine, and protein catabolic rate. *Side effects:* hyperglycemia and ACTH secretion

CKD, Chronic kidney disease; *HD*, hemodialysis; *PD*, peritoneal dialysis.

patented, but still it is too early to be able to apply these therapies in the clinical setting. In any case, hypertriglyceridemia- [120], inflammation- [81], and obesity- [121] associated hypothalamic leptin resistances need consideration and may explain the so far unsuccessful attempts with this hormone in human obesity. Given that some drugs such as cannabinoids, corticosteroids, or pentoxifylline exert both antiinflammatory and appetite stimulant effects, interventional studies are needed to assess its clinical application in the management of appetite and food intake in ESRD.

Conclusion

Poor appetite is a common finding in ESRD patients. Anorexia leads to PEW and associates with worse clinical outcomes, including hospitalizations, quality of life, and death. Appetite regulation in ESRD is complex and multifactorial in origin. It is possibly initiated by the reduction in kidney function per se but later on evolves in a complex pathophysiology involving not only uremic toxin retention but also metabolic dysregulation alterations in the organs involved in nutrient intake and utilization as well as clinical depression. Regular enquires about patient's appetite by the nephrology team is warranted for early detection and appropriate management. At present, such management may require a thorough screening (and treatment) of underlying causes. Evidence on the use of appetite stimulants so far is scarce and limited to megestrol acetate.

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CHAPTER

49

Herbal supplements in patients with kidney disease

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Introduction

The impact of herbal supplements on kidney function as well as the interaction between herbal supplements and commonly used treatments for patients with kidney disease will be reviewed in this chapter. Herbal medicine, as defined by Jonas and Levin in the *Essentials of Complementary and Alternative Medicine*, is "a healing approach that uses medicinal plants singly or in combination to treat disease and as a preventive to promote health and well-being" [1]. Any form of the plant or plant product can be included in this definition; for example, the leaves, stem, flowers, roots, seeds, or even extract of the plant can be used to enhance health.

It is difficult to pinpoint the exact number of adults who use herbal medicines; part of the difficulty stems from a variety of terms used in research surveys. However, the use of herbal medicine in the general population, and specifically in those patients with chronic diseases, is thought to be very high. In a 2016 report from the Centers for Disease Control and Prevention, adults spent $28.3 billion out-of-pocket on complementary health approaches; individuals with family incomes spent between $50,000 and 9999 on such natural products ($4.1 billion) as nonvitamin, nonmineral dietary supplements [2]. In both 2007 and 2012 the National Health Interview Survey reported that natural products were the most frequently used complementary health approach among adults and children; almost 18% of American adults and 5% of children used these products [3]. Of the adults using natural products, fish oil or omega-3 fatty acids were the most popular, at 7.8%.

Herbal medicine is often considered by the general public to be "more natural" and therefore "safe" when compared to conventional medicine. Unfortunately, this way of thinking is flawed. Many of the herbal products on the market today have multiple ingredients, and these ingredients may or may not be present in sufficiently high concentrations to be pharmacologically active. An example of a herbal product having multiple chemicals was highlighted by Dr. Stephen Bent in a paper from the University of California, San Francisco Medical Center [4]. In this paper, Dr. Bent describes ginkgo biloba as containing at least 33 different chemicals.

In contrast to medications the Dietary Supplement Health and Education Act, passed in 1994, allows herbal medicines to be produced and sold without evidence of safety or efficacy. In fact, of the most commonly purchased herbal products sold in the United States, only 5 out of 10 products have evidence of efficacy (i.e., ginkgo biloba, garlic, St. John's wort, soy, and kava kava) [4]. It should be noted that even the evidence for safety and effectiveness that does exist for individual herbal products has major limitations with regard to the information provided, concerning the methods for preparing the product, the methods for testing, and the primary outcomes from clinical studies on the product.

There are three basic ways in which herbal medicines may be unsafe: (1) due to the presence of contaminants [5]; (2) due to the presence of biologically active compounds; and (3) due to herbal-to-drug or herbal-to-herbal interactions. A recent example of the risk of contamination was outlined in a case study by Prakash et al. [5] where a patient presented with a significant decline in renal function and an abnormal presentation of symptoms. Upon investigation, it was discovered that the patient had been

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consuming an Ayurvedic herbal product from India. Each tablet of this herbal product had 236.7 μmol (49,000 μg) of lead, which had resulted in lead poisoning and subsequent rapid progression of kidney failure in the patient.

A well-documented negative effect of a biologically active compound, aristolochic acid, has been shown to cause Fanconi's syndrome nephropathy, characterized by proximal tubular toxicity, increased low molecular weight proteins in urine, and chronic renal interstitial fibrosis [6]. This compound was incorporated in Chinese herbals used for weight loss. In a case study describing 105 Belgium women taking the Chinese herbal, 43 developed end-stage renal disease and 39 underwent prophylactic nephrectomy [7].

Finally, with multiple chemical compounds in the herbal medicines, some of which are biologically active, it is not difficult to understand why there is a risk that these products may interact with drugs, foods, and other supplements. Herbals can interfere with absorption, metabolism, and potentially the excretion of other metabolites found in conventional medicines and in nutrients from food [1]. A classic example of a herbal product interacting with metabolism is St. John's wort that is degraded by the cytochrome P450 enzyme system in the liver and thus interferes with the metabolism of other drugs that are processed by the same system.

To more completely understand herbal metabolism, a brief discussion of the cytochrome P450 enzymatic system may be worthwhile, as both St. John's wort and aristolochic acid are nephrotoxic and are metabolized by this system. Cytochrome P450, a detoxifying system with subclasses that metabolize foreign toxins, is the most important xenobiotic-metabolizing enzyme system and is found primarily in the liver [8]. However, there are both cytochrome P450 systems and non-P450 enzymes in the kidney as well. This enzyme system is responsible for metabolizing many commonly used medications, such as morphine-derived pain-reducing agents, oral contraceptives, and chemotherapeutic agents [4].

The following is an overview of herbal supplements and how they relate to the kidney, with specific emphasis on acute kidney injury, chronic kidney disease (CKD), and kidney transplantation.

Acute kidney injury

The acute effects on kidney function and injury of different herbal products, as described in various publications, are summarized in Table 49.1. This table illustrates the variety of reasons why people take these supplements, from weight loss to constipation to diabetes, and the wide range of biological chemicals that have potentially negative side effects related to kidney health and function.

Aristolochic acid nephropathy

Aristolochic acids are a family of structurally related compounds that are not uncommonly referred to as simply aristolochic acid. The adverse effects of aristolochic acids on the kidney are so characteristic and well documented that they have a proper name: aristolochic acid nephropathy (AAN). This type of nephropathy, previously called Chinese herbal nephropathy, usually presents with subacute renal failure with severe anemia or as Fanconi's syndrome and often results in rapid progression to end-stage renal disease [19,20]. Histological examination of the kidney with AAN indicates interstitial nephritis with severe fibrosis. The chronic kidney failure may be complicated by neoplastic transformation in the urothelium. Aristolochic acid is considered to be the cause of Balkan endemic nephropathy [8]. The products of aristolochic acid metabolism by cytochrome P450 are called aristolactums and are primarily found in urine and feces. It is unknown whether these metabolites are the cause of AAN or whether the aristolactums are further metabolized by the kidney, and the subsequent products of this metabolism cause the toxicity (see Fig. 49.1).

In 2001 the US Food and Drug Administration published a list of products containing aristolochic acid as a warning to consumers (see Table 49.2). On April 23, 2019 an alert was published by the Food and Drug Administration regarding aristolochic acid and its danger for kidney injury (https://www.accessdata.fda.gov/cms_ia/importalert_141.html). This alert indicates that some manufacturers of food supplements still include aristolochic acids in their products, and that consumers and health-care providers need to be aware.

Herbal teas

Chronic kidney disease

The use of herbs in the dialysis population is a particularly difficult challenge for both patients and health-care providers in terms of determining their safety and effectiveness. There is a paucity of data describing herbal excretion, dialytic clearance, and interaction with other drugs. In a 2007 study by Duncan et al. [21], dialysis patients were surveyed on complementary and alternative medicine (CAM) use. A total of 294 patients were given paper surveys, and 153 patients completed the survey (52%). Of the

TABLE 49.1 Herbal supplements and acute kidney injury.

Active compound	Herb/plant	References	Reason for use	Symptoms	Other
Aristolochic acid	*Akebia* species, Boui, Mokutsu, Mu-tong, *Aristolochia* species (*Stephania* species)	Isnard Bagnis et al. [6]	Ingredient in herbal "slimming pills," Chinese herbals for hepatitis B	Aristolochic acid-nephropathy: Fanconi's syndrome, increased low-molecular weight proteins in urine, chronic interstitial renal fibrosis, proximal tubular toxicity	Also a risk factor for carcinomas of the urinary tract in animals and humans
Aloesin (aloeresin A/B)	*Cape aloes*	Luyckx et al. [6,9]	Laxative	Acute oliguric renal failure, interstitial nephritis (intervenous, IV administration)	
Sciadopitysin	*Taxus celebica*	Lin et al. [6,10]	Diabetes therapy	Acute tubular necrosis, fever, gastrointestinal (GI) upset, hemolysis	
Atractyloside	*Callilepis laureola*	Seedat and Hitchcock [6,11]	Vermifuge or purgative (Zulu)		
Glycyrrhizic acid/ glycyrrhetinic acid	*Glycyrrhiza glabra*, *Glycyrrhiza radix* (licorice), *Glycyrrhiza uralensis* (gancao)	Stewart et al. [6,12]	Cough mixtures, teas	Aldosterone-like effect, inhibition of renal steroid dehydrogenase enzyme, proximal tubulopathy	
Glycyrrhizic acid, aristolochic acid	Boui-ougi-tou (Chinese herbs/drugs mixture)	Stewart et al. [6,12,13]	Cure for obesity	Fanconi's tubulopathy	
Ephedrine	Ma huang (usually as tea)	Powell et al. [14]	Asthma, cold/flu, fever/chills, aches, edema	Hypertension, kidney stones	
Anticholinergic substances (scopolamine, hyoscyamine, atropine)	*Datura metel*, *Rhododendron molle*	Chan et al. [15]		Acute urine retention	
	Vaccinium macrocarpon (cranberry)	Harkins et al. [16]		Oxalate stones in high-risk patients	
Paraphenylenediamine	Takaout roumia	Isnard Bagnis et al. and Sir Hashim [6,17]	Substitute for *Tamaris orientalis* in hair dye	Acute tubular necrosis, rhabdomyolysis	
Sodium or potassium dichromate	Substituted for herbal ingredients	Wood et al. [18]		Acute renal failure, albuminuria, pyuria, hematuria, interstitial nephritis	

responders, 18% said they were currently using some form of CAM, 63% indicated they would be willing to try a type of CAM, and 19% said they would never use CAM. Of those who were currently using CAM, the most consumed herbals were St. John's wort, ginkgo, vitamin B_{12}, and melatonin. While these findings are interesting, the study sample was quite small with only 12 patients in the CAM user group. Thus the data cannot be generalized to the larger hemodialysis population. However, this study does highlight the importance of a thorough assessment of CKD and chronic dialysis patients to identify their use of herbal supplements. Table 49.3 outlines herbs that may affect CKD patients who are receiving dialysis.

Five herbals with some proven efficacy

St. John's wort

St. John's wort is primary used as an antidepressant and multiple randomized clinical trials have shown it to be effective in relieving mild-to-moderate depression. A metaanalysis was conducted by Linde et al. [39], which reviewed the pertinent clinical trials to determine whether the active ingredient in St. John's

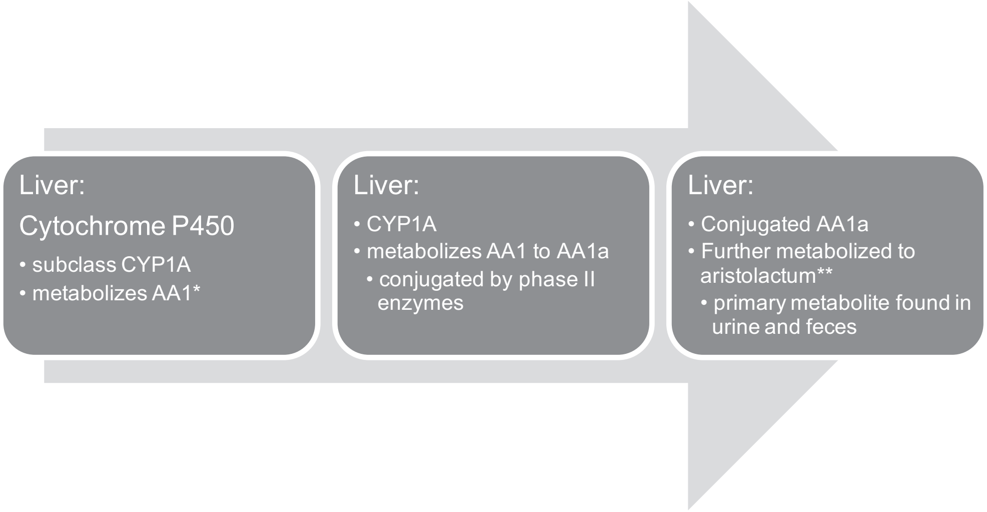
Liver:
Cytochrome P450
• subclass CYP1A
• metabolizes AA1*
Liver:
• CYP1A
• metabolizes AA1 to AA1a
• conjugated by phase II enzymes
Liver:
• Conjugated AA1a
• Further metabolized to aristolactum**
• primary metabolite found in urine and feces

FIGURE 49.1 Metabolism of aristolochic acid. *Aristolochic acid 1, the most toxic derivative of aristolochic acid. **Exact location of this action is not known, possibly both the liver and kidney. *Adapted from Xiao Y, Ge M, Xue X, Wang C, Wang H, Wu X, et al. Hepatic cytochrome P450s metabolize aristolochic acid and reduce its kidney toxicity. Kidney Int 2008;73(11):1231−9.*

TABLE 49.2 The Food and Drug Administration list of herbal products containing aristolochic acid.

Product name	Manufacturer/distributor
Rheumixx	PharmaBotanixx, Irvine, CA (Distributor), Sun Ten Laboratories, Inc., Irvine, CA (Manufacturer)
Bioslim	Doctor's Natural Weight Loss System Slim Tone Formula: Thane International, La Quinta, CA (Distributor)
Prostatin	Herbal Doctor Remedies, Monterey Park, CA (Distributor)
Fang Ji Stephania	Lotus Herbs Inc., La Puente, CA (Distributor)
Mu Tong *Clematis armandii*	Lotus Herbs Inc., La Puente, CA (Distributor)
Temple of Heaven Chinese Herbs Radix aristolochiae	Mayway Corporation, Oakland, CA (Distributor) and Almira Alchemy, Alachua, FL (Distributor)
Meridian Circulation	East Earth Herb Inc. (Brand name Jade Pharmacy), Eugene, OR
Qualiherb Chinese Herbal Formulas Dianthus Formulas Ba Zheng San	QualiHerb (Division of Finemost), Cerritos, CA (Distributor)
Clematis & Carthamus Formula 21280 (two samples)	QualiHerb (Division of Finemost), Cerritos, CA (Distributor)
Virginia Snakeroot, Cut *Aristolochia serpentaria* (two samples)	Penn Herb Co. Ltd., Philadelphia, PA (Manufacturer)
Green Kingdom Akebia Extract	Green Kingdom Herbs, Bay City, MI (Manufacturer) Ava Health, Grove City, OH (Distributor)
Green Kingdom Stephania Extract	Green Kingdom Herbs, Bay City, MI Ava Health (Distributor)
Neo Concept Aller Relief	BMK International, Inc., Wellesley, MA (Distributor), Sun Ten Labs, Irvine, CA (Manufacturer)
Mu Tong *C. armandii*	Botanicum.com, Winnipeg, Canada and Pembina, ND
Fang Ji Stephania	Botanicum.com, Winnipeg, Canada and Pembina, ND
Stephania tetrandra, roots, whole [1]	Ethnobotanical, Racine, WI

Product labeling states "Not for human consumption."

See http://wayback.archive-it.org/7993/20171114232638/https://www.fda.gov/Food/RecallsOutbreaksEmergencies/SafetyAlertsAdvisories/ucm095272.htm [accessed 08.10.11], *page last updated on May 5, 2009.*

TABLE 49.3 Herbal supplements with that may affect chronic dialysis patients.

Supplement	References	Claimed benefits	Risks/side effects/drug interactions	Kidney effects	Other
Garlic (*Allium sativum*)	ADA Dietary Supplements, Natural Medicines Database, Banerjee et al. [22]	Reduces cholesterol, reduces blood pressure, treats *Helicobacter pylori* infection, treats diarrhea, prevents cancer, treats diabetes, immune system stimulation, reduces blood pressure	May increase bleeding time, should be used with caution before surgery because of anti-aggregation effects, especially with warfarin, ginger, ginkgo. Decreases cytochrome P450 enzyme substrates: cyclosporine, some calcium channel blockers. Decreases efficacy of antiretrovirals especially protease inhibitors: do not combine. In rats, high doses have been shown to be toxic perhaps due to prooxidant effects, or inhibition of alkaline phosphatase or alcohol dehydrogenase. High doses of garlic homogenate can change the cellular architecture of kidneys in rats. May cause GI distress	Shown to decrease lipid peroxidation in heart, kidney, and liver in rats fed with red garlic homogenate. May lower blood lipids, particularly oxidized LDL through enhanced nitric oxide production. Some animal studies have indicated that garlic is renoprotective when administered before known nephrotoxins	Many types of garlic preparations; they have different properties and efficacy because of different chemical compositions from processing
St. John's wort (*Hypericum perforatum*)	ADA Dietary Supplements, Shibayama et al. [23], Natural Medicines Database	Reduces depression, increases well-being. Does seem to have positive effects similar in scope to antidepressants in patients with moderate depression. Mixed results in major depression	GI symptoms, dizziness, headache, hypoglycemia, photosensitivity are side effects. Should not be used by individuals with Alzheimer's. Abrupt discontinuation may cause anxiety, headaches, and insomnia. Causes hypotension in anesthesia. Additive effects with antidepressant drugs may be dangerous. Decreases effectiveness of contraceptives, protease inhibitors, digoxin, antiepileptics, antipsychotics, immunosuppressives, and anticoagulants. Does not combine with drugs metabolized through the cytochrome P450 pathway, including	Pretreatment with St. John's wort has been shown to reduce cisplatin nephrotoxicity in rats with normal baseline kidney function. How this translates to humans/CKD is unclear	Multiple reports of organ transplant rejection after cyclosporine + St. John's wort

(*Continued*)

TABLE 49.3 (Continued)

Supplement	References	Claimed benefits	Risks/side effects/drug interactions	Kidney effects	Other
			beta-blockers, antiinflammatories, also does not combine with phenobarbital, phenytoin (speeds metabolism of both, decreases seizure control) and narcotics		
Ginseng (*Panax ginseng*, *Panax japonicus*, *Panax qinquefolius*, *Eleutherococcus senticosus*) active compound is saponins ginsenosides	ADA Dietary Supplements, Natural Medicines Database, Liao et al. [24], Kim et al. [25], Roemheld-Hamm and Dahl [26]	Improves exercise, QOL, energy, mood, sexual function, helps control blood glucose levels	Extremely high doses 3 g root per day (or 600 mg extract) may cause hypertension, edema, so lower doses are safe for up to 4 weeks. *E. senticosus* (Siberian ginseng) is contraindicated for HTN. Changes blood coagulation, unclear if inhibits or encourages platelet aggregation but does not combine with warfarin. Interacts with corticosteroids, digoxin, furosemide, diabetes medications (due to blood glucose–lowering effects). Has mild hormone effects, can interfere with contraceptives, hormone therapy, avoid if history of estrogen-related cancers. Some reports of insomnia, perhaps due to stimulant effects	Study in rats with streptozotocin-induced diabetes showed lower blood glucose levels and less diabetic nephropathy (lower creatinine and urinary protein levels compared to controls) when fed heat-treated American ginseng. The case report of an 83-year female with renal insufficiency experiencing brachycardia and increased digoxin levels after ingestion of ginseng for approximately 1 month. Ginseng is known to increase digoxin, perhaps due to their similar structures. The kidneys are the main organ responsible for digoxin removal	Reports of contaminated ginseng products: 8/20 had high levels of pesticides, 2/20 had lead levels, and 7/20 had low levels of ginsenosides (active compounds)
Ginkgo biloba	ADA Dietary Supplements, Kim et al. [27], Natural Medicines Database	Improves memory and circulation	May cause GI upset, including diarrhea, nauseas vomiting at high doses. Interacts with seizure medications, can decrease clotting when on anticoagulant drugs but may also increase the risk of intercranial bleeding. Interacts with certain antidepressants (buspirone, fluoxetine, St. John's wort) to create hypomania. Reduces the efficacy of thiazide diuretics, should not be combined with	Study in 33 PD patients showed that ginkgo biloba extract (150 mg/d for 8 weeks) decreased D-dimer levels compared to the control group. No changes in bleeding time, albumin, or CRP were noted; however, one patient dropped out due to GI side effects	Ginkgo seeds are poisonous, leaves are used

(*Continued*)

TABLE 49.3 (Continued)

Supplement	References	Claimed benefits	Risks/side effects/drug interactions	Kidney effects	Other
			anticonvulsants as the ginkgo toxin can cause seizures, can also change the action of diabetes drugs, can cause spontaneous bleeding when combined with ibuprofen		
Melatonin	ADA Dietary Supplements, Herrera et al. [28], Koch et al. [29,30], Natural Medicines Database	Regulates circadian rhythms, including in jet lag, helps with migraines, reduces cancer risk, and enhances sex drive	Long-term effects unknown, seems safe in short term. Can interfere with immunosuppressive drugs and other sleep medications. Use caution when combining with antidiabetic drugs, anticoagulant drugs, central nervous system depressants (additive sedative effects)	Nine new HD patients receiving IV iron, and ruHEPP had increased oxidative stress compared to matched controls but those who were administered oral melatonin (0.29 mg/kg) 1 h prior to EPO had lower measures of oxidative stress compared to those who received to placebo before EPO (lower plasma malondialdehyde, RBC glutathione, and catalase). In 20 daytime HD patients, crossover design 3 mg melatonin administered at 10 p.m. for 6 weeks improved subjective and objective measures of sleep time and quality and nights of dialysis and nondialysis days	
CoQ10 (ubiquinone)	ADA Dietary Supplements, Shojaei et al. [31]	Antioxidant effects claimed: improve health in heart disease, HTN, exercise, cancer, prevent migraines	GI distress, including appetite suppression, vomiting, diarrhea, nausea, may occur. May reduce the efficacy of warfarin and have an additive effect with antihypertensives	CoQ10 when administered alone or in combination with carnitine for 3 months lowered lipoprotein(a) levels in HD patients on statins compared to those on statins only. No adverse effects were noted	Smoking, HMG-COA reductase drugs may deplete body stores. B-6 is required for endogenous synthesis
Noni juice (from *Morinda citrifolia*)	ADA Dietary Supplements, Natural Medicines Database	Prevents cancer, increases immunity, reduces BP, reduces cholesterol levels, pain relief, controls diabetes	Potassium content similar to orange juice, risk of hyperkalemia; should not be combined with ACE inhibitors, ARBS, and potassium-sparing diuretics. May also reduce efficacy of warfarin, reports of hepatotoxicity from Noni juice consumption, reversed with the termination of consumption		
Echinacea (*Echinacea angustifolia*, *Echinacea pallida*, *Echinacea purpurea*)	ADA Dietary Supplements, Natural Medicines Database	Boosts immune function, protects against colds and URI, UTIs, yeast infections	Can cause fever, GI upset, taste alterations, dry mouth, headache, dizziness, insomnia. Patients with grass allergies should use with caution as anaphylaxis has been reported. Decreases efficacy of immunosuppressants, should be avoided in patients with autoimmune diseases, also not to be combined with hepatotoxic medications. Can increase plasma levels of caffeine by 30% due to inhibition of cytochrome P450, should avoid with other cytochrome P450 substrate drugs		
Glucosamine	ADA Dietary Supplements, Natural Medicines Database	Reduces pain in joints from osteoarthritis by protecting and producing collagen, and other cartilage components. Mixed results: may be safer than others, but as effective as NSAIDS, other studies show no results	May impact blood glucose control, should monitor patients with DM. Patients with shellfish allergy should not consume. Additive effect with warfarin, should not be combined	Anecdotal reports of induced renal toxicity	

(*Continued*)

TABLE 49.3 (Continued)

Supplement	References	Claimed benefits	Risks/side effects/drug interactions	Kidney effects	Other
Ginger (*Zingiber officinale*)	ADA Dietary Supplements, Natural Medicines Database, Onwuka et al. [32], Shanmugam et al. [33]	Antinausea (pregnancy, chemo, postsurgery), loss of appetite, treats migraines	May increase the effect of anticoagulants and glucose-lowering drugs (may increase blood glucose). May have additive effect with calcium channel blockers	Animal studies indicate that it is a protective antioxidant compound against oxidative and nephrotoxic agents, including cadmium, with statistically significant decreases in lipid peroxidation and kidney damage (shrinkage) in rats compared to cadmium treated without ginger. It also protects against alcoholic kidney damage, including reversing tubule degeneration at a dose of 100 mg/kg/d ginger extract for 30 days	GRAS status
Soy	Roemheld-Hamm et al. [26], Imani et al. [34], Siefker and DiSilvestro [35]	Menopause symptoms, hypocholesterolemic, antioxidant, antiinflammatory properties	May lower coagulation factor IX. Soy isoflavones may be elevated in patients on dialysis treatment as they are not well cleared	Studies indicate soy lowers cholesterol and blood pressure	
Flaxseed	ADA Dietary Supplements, Sankaran et al. [36]	Laxative, manages IBS symptoms, improves blood lipids, improves inflammatory symptoms, reduces heart disease risk	Requires extra fluid consumption (150 mL/10 g flaxseed) or risk of impaction; may interact with warfarin therapy. Flaxseed lignins are a phytoestrogen and their effect on hormone-sensitive cancers is unclear, may compete for uptake with exogenous hormones like contraceptives. Flaxseed may have anticoagulant effects (through $n-3$ fatty acid prostaglandin pathway), concerns for surgical bleeding, and additive effects with anticoagulant medications. May increase triglycerides in individuals with hypertriglyceridemia. May have additive effect with glucose-lowering drugs, high	Flaxseed oil–based diets in diabetic rats and mice with PKD have prevented renal injury when initiated early in the disease state, but when initiated later (2 months in PKD rats, similar to stage 3 CKD) renal injury is not ameliorated, but inflammation is reduced	

(*Continued*)

TABLE 49.3 (Continued)

Supplement	References	Claimed benefits	Risks/side effects/drug interactions	Kidney effects	Other
			fiber content may also inhibit the absorption of other drugs, including furosemide		
Black cohosh (*Cimicifuga racemosa*)		ADA Dietary Supplements, Roemheld-Hamm et al. [26]	Reduces premenstrual and postmenopausal symptoms	Although not a hormone, it affects hormones so should be avoided in women with breast cancer or who are pregnant. GI upset may occur, may also cause weight gain, cramping. Long-term use discouraged, may be safe for up to 6 months. Must be avoided in individuals with existing liver disease or who are taking hepatotoxic drugs due to its potential hepatotoxicity (49 reports of hepatotoxicity). May inhibit cytochrome P450, so should be avoided with substrate drugs, one case report of negative effects when combined with Lipitor	
Remifemin is the brand name of standardized extract					
Lutein	ADA Dietary Supplements, Sundl et al. [37]	Treats age-related macular degeneration and cataracts	No data on drug interactions. So far proven safe and effective even with long-term use	PD patients have been found to have lower lutein levels (and other carotenoids) than healthy matched controls and within PD patients lower carotenoid status correlates with higher inflammatory markers. No research on how lutein supplementation affects these parameters	
Milk thistle (*Silybum marianum*)	ADA Dietary Supplements, Vessal [38], Natural Medicines Database	Improves liver health, including treating viral hepatitis and alcoholic cirrhosis, improves appetite, is used to manage diabetes	GI upset, including nausea, diarrhea, allergic reactions, may occur. May interact with antiretrovirals, cytochrome P450 metabolized drugs, may speed clearance of statins, diazepam, digoxin, morphine. May chelate iron	Milk thistle extract, fed for 4 weeks at 1.2 mg/kg to streptozotocin-induced diabetic rats lead to lower serum glucose, serum urea, higher eGFR, and lower 24-h urinary protein than streptomycin diabetic rats not receiving the supplement and did not affect the parameters of control (nondiabetic) rats who received the supplement. The silymarin itself (100 mg/kg) improved parameters in the diabetic rats but was not statistically significant. It is suggested that the mechanism is through ROS scavenging	
Saw palmetto (*Serenoa repens*)	ADA Dietary Supplements, Natural Medicines Database	Improves enlarged prostate, prevents prostate cancer, prevents male alopecia, diuretic, antiinflammatory	Anticoagulant, should be discontinued before surgery. Should not be mixed with other anticoagulant medications. May interact with hormone medications through antiestrogenic effects		

ARBS, angiotension receptor blockers; *CKD*, Chronic kidney disease; *CRP*, C-reactive protein; *eGFR*, estimated glomerular filtration rate; *EPO*, erythropoeitin; *GI*, gastrointestinal; *GRAS*, generally regarded as safe; *HD*, hemodialysis; *IBS*, inflammatory bowel syndrom; *IV*, intravenous; *LDL*, low-density lipoprotein; *NSAIDS*, nonsteroidal anti-inflammatory drugs; *PD*, peritoneal dialysis; *PKD*, polycystic kidney disease; *rHuEPO*, recombinant human erythropoietin; *ROS*, reactive oxygen species; *URI*, upper respiratory infection; *UTI*, urinary tract infection; *QOL*, quality of life.

wort was effective in reducing mild or moderate depression. To be included in this analysis the study had to meet the following criteria: (1) randomized and double-blind; (2) patients with depressive disorders; (3) compared extracts of St. John's wort with placebo or standard antidepressants; and finally, (4) clinical outcomes such as scales assessing depressive symptoms. A total of 37 clinical trials were ultimately included in the metaanalysis. The St. John's wort was more effective in moderate or mild depression than in severe depression. The relative risk for the reduction of depression symptoms by St. John's wort from six larger trials was 1.71 (95% CI, 1.40–2.09) and from five smaller trials was 6.13 (95% CI, 3.63–10.38) [39].

The primary active ingredients in St. John's wort are hypericin and pseudohypericin. The mechanism of both hypericin and pseudohypericin related to improving mild and moderate depression is the inhibition of reuptake of serotonin into the central nervous system [40]. It may be hypothesized that depression is caused by a reduction in the functional activity of monoamines such as the centrally acting neurotransmitters: serotonin, dopamine, and norepinephrine. Inhibition of the reuptake of serotonin by St. John's wort results in increased concentration of serotonin in specific nerve synapse and thus improves functionality of serotonin.

Bioavailability of St. John's wort is poor; it is estimated at 14% for hypericin and 21% for pseudohypericin [40]. Excretions of these compounds in St. John's wort are through the kidneys, and the half-life is 25−26.5 hours for hypericin and 16−36 hours for pseudohypericin [41].

In the non-CKD population an effective dose consists of 300−900 mg of the plant extract per day due to the variability in concentration from 0.2% to 2.5% of hypericin [41]. However, no data were found concerning the safe dose for CKD patients. It is possible that in end-stage renal disease patients, St. John's wort compounds may accumulate in the body since the typical route of excretion is no longer available, but there are no data to confirm this possibility.

Side effects in people taking St. John's wort are rare and may include photosensitivity. However, drug interactions are a concern. St. John's wort may interfere with the action of monoamine oxidase inhibitors and selective serotonin reuptake inhibitors; it may antagonize reserpine and reduce serum concentrations of cyclosporine, indinavir, and possibly other drugs used to control HIV infection. Additionally, the active compounds may reduce estrogen concentrations from oral contraceptives, decrease the efficacy of digoxin, irinotecan, other cancer treatment drugs, and seizure control drugs, such as Dilantin and phenobarbital. Finally, warfarin and related anticoagulants may be affected by St. John's wort [21]. Due to the effects on cyclosporine, transplant patients must be monitored closely for use of this herb, and doses of either the cyclosporine or St. John's wort may need to be altered to prevent risk of rejection.

Garlic: *Allium sativum*

The reported benefits of garlic are on such risk factors for cardiovascular disease as reduced serum lipid concentrations [total cholesterol, low-density lipoprotein (LDL), and triglycerides] and blood pressure, increased fibrinolytic activity, antibiotic properties, enhanced activity of natural killer cells, and lengthened clotting time [21,40]. In the non-CKD population, randomized clinical trials demonstrate the effectiveness of garlic as a hypocholesterolemic supplement. Kannar et al. [42] conducted a 12-week, double-blind, randomized clinical trial in patients with hypercholesterolemia. All patients received dietary counseling on a low-fat intake and then the treatment group received an enteric coated garlic powder tablet, while the other arm received a placebo. The treatment tablet contained 9.6 mg of allicin. The treatment group ($n = 22$) had a significant reduction in total cholesterol (−0.36 mmol/L) and LDL (−0.44 mmol/L), while the placebo group did not change significantly.

A metaanalysis was conducted by Jepson et al. [43] to assess the effects of garlic for the treatment of peripheral arterial occlusive disease; unfortunately, only one study met the inclusion criteria, and it was small without statistically significant results. No clinical trials testing the efficacy or safety of garlic in dialysis patients were found.

Due to the effects on clotting time, patients who are on anticoagulant medications such as heparin, Coumadin, or even aspirin may be at risk. Additionally, patients who are scheduled for surgery should be advised to withhold the consumption of garlic prior to the procedure [44].

The active ingredient in garlic is allicin, an organic disulfide, which is formed when the substance, alliin, in garlic cloves is crushed or pressed. Crushing the garlic clove releases the enzyme alliinase that converts alliin into allicin. When interpreting data on garlic as an intervention, it is important to know the amount of active allicin in the garlic preparation. Allicin is metabolized in the liver to an inactive compound and eliminated. Since garlic is metabolized and eliminated by the liver, it may be safe for CKD patients to consume garlic for cholesterol and blood pressure as long as increased time for blood clotting is monitored (see Fig. 49.2).

The mechanism of garlic as a lipid-lowering agent is not well understood; however, it is hypothesized that allicin reduces the activity of HMG-CoA reductase. HMG-CoA reductase is an enzyme in the initial step of

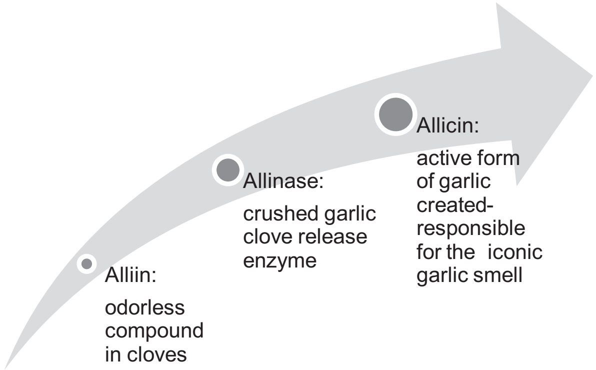
Alliin:
odorless compound in cloves
Allinase:
crushed garlic clove release enzyme
Allicin:
active form of garlic created-responsible for the iconic garlic smell

FIGURE 49.2 Formation of active compound, allicin, in garlic cloves.

cholesterol synthesis; therefore allicin may reduce endogenously manufactured cholesterol.

Ginkgo

Ginkgo biloba has been used to improve or stabilize mental function, enhance memory, and improve cerebral and peripheral disease. Ginkgo biloba was tested in 66 chronic peritoneal dialysis patients by Kim et al. [27] to determine whether the herb improves hemostatic factors and inflammation. The patients were randomized to either a control group or to receive ginkgo biloba, 160 mg/d, for 8 weeks. At the baseline of the study, there were no statistically significant differences between the control and ginkgo biloba groups for age, gender ratio, presence of diabetes and cardiovascular disease, and dialysis vintage. At the end of 8 weeks, the only parameters that changed significantly were the plasma D-dimer concentrations, which are an index of fibrin turnover and intravascular thrombogenesis. Plasma D-dimer levels decreased from 0.92 ± SD 0.59 to 0.75 ± 0.48 μg/mL ($P < .05$) in the ginkgo-treated group but did not change significantly in the control group. It may be that an active component of ginkgo biloba affects coagulation factors and thus the D-dimer levels.

Since ginkgo biloba may cause extended clotting times, patients undergoing surgical procedures or using anticoagulating medications, such as heparin, should discontinue the use of ginkgo biloba or at least have their coagulation parameters closely monitored. Other potential side effects of ginkgo are gastrointestinal complaints such as constipation, diarrhea, nausea, and abdominal pain, headache, and allergic skin reactions [44].

Soy

Soy contains high amounts of isoflavones and phytoestrogens. Women with end stage renal disease (ESRD) may be particularly interested in soy products due to its reported effects on reducing menopausal symptoms, such as hot flashes. The phytoestrogens in soy products are thought to be responsible for reducing the menopausal symptoms in addition to their potentially beneficial effects on osteoporosis and cardiovascular disease prevention. Furthermore, are sufficient data demonstrating efficacy of soy food products for cholesterol reduction to warrant statements indicating this effect on food labels.

Recently, a few small trials have been published on soy supplementation in chronic dialysis patients. An unblinded, randomized trial was conducted [34] on the effect of soy on plasma-coagulating factors. This study included 36 chronic peritoneal dialysis patients (18 on soy and 18 as control) who were followed for 8 weeks. The soy group received 28-g packets of raw, textured soy flour providing 14 g of soy protein, and 233 mg of phosphorus. Patients were not included in the study if their baseline serum phosphorus was greater than 5.5 mg/dL. At baseline, there were no significant differences in any demographic characteristics except for supplemental vitamin B_{12} intake (more patients were taking vitamin B_{12} in the soy group). At the end of the 8-week period, there was no statistically significant difference in serum phosphorus, as might be expected [soy group 3.5 ± 1.0 mg/dL (mean ± SD) vs control 3.7 ± 0.9 mg/dL]. However, there was a significant decrease in plasma coagulation factor IX (baseline soy group 135% ± 33.5% activity vs 8-week 112.5% ± 32% activity). This decrease in plasma coagulation factor IX may constitute a risk factor for patients undergoing chronic dialysis, especially if they are receiving other anticoagulating medications or herbal supplements.

Another small trial, this one in hemodialysis patients, used soy verses whey protein and tested the safety and efficacy of these different proteins on serum oxidized LDL concentrations. The study randomized 17 hemodialysis patients to receive either soy ($n = 7$ patients, 25-g protein and 52-mg flavones) or whey ($n = 9$ patients) for 4 weeks. There were no statistically significant changes in laboratory values between pre and postintervention in either group, except for serum creatinine that significantly decreased in the whey group. A significant difference in the mean change in serum oxidized LDL concentrations was found between the groups, with the serum levels in the soy group decreasing by 31.02%, and the levels in the whey group increasing by 11.12% ($P < .05$) [35].

In 2016 a systematic review and metaanalysis was published on the effect of soy protein containing isoflavones on clinical outcomes in CKD patients. There were 12 studies with 280 patients included in the final analysis that comprised both nondialyzed advanced CKD and chronic dialysis patients. The analysis indicated that the intake of soy protein was associated with a statistically significant reduction in serum creatinine, phosphorus, and C-reactive protein, and in proteinuria in the advanced CKD patients. No changes with the intake of soy protein were detected in the chronic dialysis patients; however, when the two groups of nondialyzed CKD and chronic dialysis patients were pooled, a significant decrease was found in serum urea nitrogen in the groups ingesting soy protein [45].

From these small studies and the more recent metaanalysis in predialysis and dialysis patients, soy use appears to have some efficacy, and in predialysis patients, it appears to have a lower risk of side effects. However, similar to the other herbal products, soy may interfere with coagulation factors. Thus careful monitoring of clotting parameters would be warranted in patients consuming high amounts of soy.

Kava kava

Kava extracts are derived from the rhizomes of a perennial shrub in the South Pacific Islands. The term kava comes from both the kava plant and the kava extracts [46] and is typically consumed as either a capsule or tablet containing either ethanolic or acetonic extracts. The active ingredients in kava are kavapyrones, also known as kavalactones, which have psychoactive properties. In the Western populations, kava kava has been used to treat anxiety. A randomized, double-blind crossover study was published in 2009 on the aqueous extract of kava [47]. The 60 adult subjects had 1 month of elevated, generalized anxiety (>10 on the Beck Anxiety Inventory) prior to enrolling in the study. During the treatment phase of the study ($\text{length} = 1$ week) the patients received five tablets of kava per day, each containing 50 mg of kavalactones. The pooled analysis across phases (using differences from pretreatment scores) demonstrated a significant effect across phases in favor of kava [$F(1.35) = 26.18$; $P < .0001$] and a strong effect size [47].

It is important to note that the previous clinical trial used the aqueous extract form of kava, and the duration of the intervention period was only 1 week. Teschke et al. [48] described several reports of the hepatic toxicity of the ethanolic or acetonic extracts of kava. In an analysis of kava kava [49], when quantitative tools for assessing causality were used, the data strongly supported a cause and effect relationship between the kava consumed and hepatotoxicity.

Therefore, although aqueous kava extract does appear to relieve anxiety in healthy adults, health-care workers should be aware, and patients must be cautioned that evidence strongly indicates an association between intake of kava extract and hepatotoxicity. Moreover, there are no clinical trials involving the effects of kava on patients with CKD.

Kidney transplantation

Patients who have received a kidney transplant need to be particularly aware of herbal supplements that are metabolized by the cytochrome P450 enzymatic system. The P450 system metabolizes some of the antirejection medications prescribed posttransplant, such as cyclosporine. Therefore the ingestion of herbals that are processed by the same enzymatic system may result in decreased drug concentrations and thus put the patient at increased risk of rejection. Some examples of herbal supplements that are acted on by the cytochrome P450 system are St. John's wort, *Echinacea*, and melatonin.

Clinical implications

As stated in the introduction of this chapter, surveys have been conducted indicating a high use of herbal supplements in both the general and CKD populations. It is not uncommon for patients to withhold information on their use of herbal supplements from health-care providers. Given the potential for contaminants and herb-to-drug or herb-to-herb interactions, it is imperative that health-care providers know what patients are consuming so that they can educate patients on potential risks and monitor patients more effectively. At present, there are no validated, CKD-specific questionnaires that include information on herbal or other CAM use. Therefore clinicians need to conduct thorough, individualized assessments that include specific questions regarding herbal use by their CKD patients.

In summary, herbal use is probably common in CKD and chronic dialysis patients. Many herbs contain active compounds that may interact with other medications or may have direct negative effects on the health of the patients. There are few studies of the administration of herbs to CKD patients. However, some studies do demonstrate both reasonable safety and some effectiveness in CKD patients; soy is an example. More trials need to be conducted with CKD patients to assure safety and determine the effectiveness of the most commonly used herbals.

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CHAPTER

50

Drug–nutrient interactions in renal failure

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Introduction

Foods and prescribed or over-the-counter medicines can interact in multiple ways. Such interactions may result in reduced or increased drug effects or in (often subtle) nutritional deficiencies. Drug efficacy may be reduced due to food-induced delayed or decreased absorption from the gastrointestinal tract. Diet or nutrients may induce or inhibit drug-metabolizing enzymes and increase or decrease the rate of metabolism of a given drug; they may also modify the first-pass effect. The rate of excretion of the drug or of active or toxic metabolites may also be altered by dietary effects.

The most commonly observed drug–food interaction is altered drug absorption from the gastrointestinal tract, usually a decrease in the rate of absorption. Less commonly, the drug absorption rate may be increased if taken concurrently with foods. Drugs can also induce certain specific nutrient deficiencies particularly for vitamins and minerals.

In patients with chronic kidney disease (CKD) or end-stage renal disease (ESRD), drug–nutrient interactions may lead to overt nutritional deficiencies particularly when the general nutritional status is poor or there are specific, obvious, or subclinical nutritional deficiencies. This chapter will focus on interactions between drugs typically prescribed to renal patients and foods, food supplements, and some herbal compounds.

Effect of food intake on drug absorption

The intestinal absorption of many drugs is slowed when administered concurrently with food, either because of delayed gastric emptying or because of dilution of the drug in the intestinal contents. Some medications, such as central α_2-adrenergic drugs, can reduce gastrointestinal motility and delay the emptying of the stomach and, hence, increase oral–fecal transit time [1]. In contrast, calcium channel blockers do not appear to affect gastrointestinal motility [2]. Table 50.1 lists several drugs that may be prescribed to patients with CKD and which may interfere with the gastric emptying rate. Table 50.2 lists drugs that are absorbed more slowly when given concurrently with meals. To optimize drug absorption, these medicines should be given 1 hour before or 2 hours after meals. However, there are a few commonly administered oral medicines that will undergo more effective absorption when administered with foods (Table 50.3). These include commonly used antihypertensives (diltiazem, felodipine, isradipine, labetalol, metoprolol, and propranolol). In most circumstances the food-dependent increase in drug absorption may enhance drug efficacy. However, serious toxic side effects may arise, such as when lithium or cyclosporine is given with foods.

Dietary contents can also reduce gastrointestinal drug uptake by inhibiting organic acid transport proteins (OATPs). Naringin and flavonoids in fruits, fruit juices, and vegetables such as grapefruit and orange juice have been shown to inhibit OATP1A2 [4]. The uptake of drugs that are transported by this protein (fexofenadine, L-thyroxine, atenolol, and ciprofloxacin) can be reduced by as much as 50% [4]. Etoposide absorption is also substantially reduced by grapefruit juice [5].

Subclinical or overt iron deficiency is commonly observed in patients with advanced CKD or ESRD. Low or empty iron stores may be caused by reduced nutrient and, hence, iron intakes as well as subtle iron losses. Iron deficiency is the most common reason for resistance to erythropoietin and other erythropoiesis-stimulating agents (ESAs) in patients with renal failure. Experimental studies have shown that administration of

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TABLE 50.1 Drugs affecting the gastric emptying rate (GER) [3].

Increase GER	Decrease GER
Metoclopramide	Anticholinergics
Reserpine	Atropine
Sodium bicarbonate	Amitriptyline
Ondansetron	Imipramine
Analgesics	
Morphine	
Pentazocine	
Isoniazid	
Chloroquine	
Phenytoin	
Aluminum hydroxide	
Phenothiazines	
Chlorpromazine	
Diphenhydramine	
Promethazine	
Sympathomimetics	
Levodopa	
Amantadine	

TABLE 50.2 Drugs undergoing reduced or delayed absorption if administered with food.

Acetaminophen	Ferrous sulfate[a]	Nifedipine
Amoxicillin	Fosinopril	Norfloxacin
Ampicillin	Furosemide	Ofloxacin
Aspirin	Glipizide	Oxacillin
Benazepril	Hydralazine[b]	Oxytetracycline[a]
Captopril	Ibuprofen	Penicillamine
Cephalexin	Indomethacin	Pravastatin
Cefaclor	Isoniazid	Ramipril
Cimetidine[c]	Ketoconazole	Rifampin
Ciprofloxacin[c]	Ketoprofen	Simvastatin
Clindamycin	Levodopa	Spironolactone
Demeclocycline	Levothyroxine[b]	Sulindac
Digoxin	Lisinopril	Tacrolimus
Doxycycline	Methotrexate	Tetracycline[a]
Enalapril	Misoprostol	Zidovudine
Erythromycin	Nicardipine	Zink salts

[a] *Mainly dairy products.*
[b] *Particularly enteral formulas, Ca-supplements or Ca-containing phosphate binders.*
[c] *Concurrent administration with caffeine-containing foods may increase caffeine uptake.*

TABLE 50.3 Drugs that are absorbed more effectively if given with food.

Buspirone	Griseofulvin
Carbamazepine	Isradipine
Cefpodoxime	Labetalol
Cefuroxime	Lithium salts
Chlorothiazide	Metoprolol
Cyclosporine	Morphine
Diazepam	Nitrofurantoin
Dicumarol	Propafenone
Diltiazem	Propranolol
Etretinate	Quinidine
Famotidine	Sertraline
Felodipine	Ticlopidine

the phosphate binder calcium carbonate ($CaCO_3$) with foods reduces the bioavailability of iron from oral iron sulfate [6]. Apparently, in the presence of calcium, iron is taken up normally into the gut mucosa, but the transfer through mucosal cytoplasm and/or basolateral membranes is reduced. This interaction is prevented by intravenous iron administration.

Roux-en-Y gastric bypass is the most common bariatric procedure for the surgical treatment of severe obesity. It results in a >90% reduction in gastric volume and in reduced functional length of the small bowel with numerous potential nutritional consequences. This may affect drug absorptions and intralumen drug–nutrient interactions.

Effects of nutrients on drug metabolism

Dietary protein and lipids

The hepatic clearance of some drugs is reduced in renal failure [7]. Drugs that are metabolized by oxidation, conjugation, or both processes may be predisposed to decreased hepatic clearance in CKD. High-protein diets can raise the activity of drugs that are metabolized through cytochrome P-450-dependent mixed function oxygenases. High-protein diets accelerate the metabolic clearance of some drugs such as theophylline and propranolol by about 30%–60% compared to low-protein diets [8].

Low-protein diets also reduce the activity of xanthine oxidase [9] and increase the plasma levels of allopurinol and oxipurinol. Since oxipurinol accounts for some of the adverse effects of allopurinol, the concurrent prescription of low-protein diets and allopurinol may increase the likelihood of allopurinol toxicity [9]. The prescription of low-protein diets to patients with CKD may also reduce the sulfate conjugation of some drugs, although clinical studies directly examining this question in patients or normal subjects are lacking. Drug sulfation depends on the availability of sulfur-containing amino acids and the possible release of sulfur in the gut by the action of intestinal sulfatases.

Cruciferous vegetables and drug metabolism

Drug metabolism can be affected by other compounds derived from certain foods. For example, various indoles that originate from cruciferous vegetables, such as cabbage and Brussels sprouts, enhance oxidation and increase the metabolic clearance rate of medicines. Such foods also may enhance drug glucuronidation in healthy subjects, for example, for acetaminophen [10]. Diet-derived compounds may affect the activity of the P-450 enzyme species by the competitive inhibition of the P-450-dependent monooxygenase system [11]. Indole-3-carbinol and related compounds that are present in cruciferous vegetables, particularly Brussels sprouts, are potent inducers of the intestinal P-450 IA1 (CYP1A1) and hepatic CYP1A1 and CYP1A2 isoenzymes [12].

Nutrients and cytochrome P-450-dependent drug metabolism

Increased dietary protein augments hepatic microsomal cytochrome P-450 content probably through tryptophan and sulfur amino acids [13]. In contrast the activity of this enzyme system is reduced by low-protein, high-carbohydrate or fat diets, flavonoids (i.e., contained in citrus fruits and some vegetables), large doses of riboflavin, and possibly during total parenteral nutrition. The cytochrome P-450IIE1 (CYP2E1) isoenzyme is induced by dietary lipids [14]. This isoenzyme participates in the metabolism of acetaminophen, enflurane, and halothane [11]. Moreover, the CYP2E1 isoenzyme is also activated by fasting as well as by thiamine deficiency [14]. Several other alterations in the micronutrient status can affect the oxidative metabolism of drugs (Table 50.4).

Large doses of vitamin C given as nutritional supplements to patients without ascorbic acid deficiency may increase the rate of oxidative drug metabolism. High vitamin C intakes can also reduce the rate of sulfate conjugation of drugs, such as acetaminophen, by competing for the available sulfate. Dietary supplementation with large doses of pyridoxine may increase the metabolism and decrease the therapeutic efficacy of levodopa, since this vitamin is a cofactor for the dopa decarboxylase [15].

TABLE 50.4 Effects of micronutrients on oxidative drug metabolism [11].

Vitamin A deficiency	**↓P-450**
	↓Metabolism of aminopyrine, Coumadin
Vitamin A, high dose	↑Metabolism of Coumadin
Niacin deficiency	↓Metabolism of anesthetics
Riboflavin deficiency	↓NADPH:P-450 reductase
	↑Aminopyrine metabolism
Vitamin C deficiency	↓P-450
	↓NADPH:P-450 reductase
	↓Monooxygenases activities
Folic acid deficiency	↓Induction of CYP2B1 by barbiturates
Aluminum, high dose	↓Hepatic P-450
Selenium deficiency	↓Induction of P-450 by phenobarbital
Zinc deficiency	↓Phenobarbital and aminopyrine metabolism

Cytochrome P-450 isoenzyme CYP3A4 activity, citrus juice compounds, and St. John's wort

Many drugs are metabolized through the cytochrome P-450 isoenzyme CYP3A4, including those used in patients with renal diseases. Some estimates suggest that CYP3A4 is involved in the metabolism of as much as half of all marketed drugs [16]. It is the broad substrate affinity that renders this isoenzyme so important as well as susceptible to activity modifications by nutrients. A few drugs utilize CYP3A4 for activation from the prodrug to the active metabolite such as clopidogrel.

This isoenzyme is expressed in liver microsomes where it contributes to drug metabolism and in the enterocyte microsomes of the small intestines where it can reduce bioavailability of substrate drugs due to first-pass effect. Compounds present in citrus juice inhibit CYP3A4, and St. John's wort (extract of *Hypericum perforatum*) induces CYP3A4 levels and activity. Flavonoids, such as naringin, are present in rather large amounts in citrus fruits, citrus juices, and some vegetables [17]. The related aglycone, naringenin, is readily formed in humans from its precursor and, like other flavonoids, inhibits the CYP3A4. A virtually complete list of the content of different flavonoids in various foods is maintained by the US Department of Agriculture and available online [17]. Grapefruit juice which is perhaps the food most potently inhibiting CYP3A4 not only contains naringenin but also psoralen derivative and other flavonoids that are also thought to inhibit this isoenzyme. Many different flavonoids can severely inhibit CYP3A4 (as much as 100% in vitro). These compounds are also found in other citrus juices and fruits, fennel, bell pepper, celery, carrots, other foods, as well as *Ginkgo biloba* [17,18]. In clinical studies, in normal subjects naringin inhibits the metabolism of the CYP3A4 substrate nisoldipine only moderately giving rise to the importance of other compounds in grapefruit juice as inhibitors of this cytochrome P-450 isoenzyme [19]. Although the effect of these grapefruit juice compounds on CYP3A4 may be clinically more important, they also tend to inhibit several other cytochrome P-450 isoenzymes such as CYP1A2, CYP2C9, CYP2C19, and CYP2D6 [18].

CYP3A4 is present in relatively large concentrations in the wall of the small intestine where it contributes to the first-pass metabolism of several drugs limiting the amount of active drug that reaches the blood stream. The inhibition of CYP3A4 by compounds in grapefruit juice and other citrus fruit juices is clinically important since this isoenzyme plays a major role in the metabolism of drugs that are commonly used in patients with CKD or ESRD. These include cyclosporine A, the dihydropyridine calcium channel blockers nifedipine, nimodipine, felodipine, nitrendipine, and nisoldipine; the calcium channel blocker verapamil; saquinavir; diazepam, midazolam, and triazolam; terfenadine and lovastatin, as well as the hepatitis C direct-acting antivirals daclatasvir, simeprevir, and telaprevir (Table 50.5) [19,20]. The bioavailability of these drugs is increased by coadministration with grapefruit juice and, perhaps, even more so in subjects consuming large amounts of citrus juices chronically (Table 50.5). For example, ingestion of diazepam, 5 mg, with 250 mL of grapefruit juice as compared to water increases the diazepam area-under-the-curve 3.2-fold [21]. The drug–nutrient interaction between compounds in citrus juices and dihydropyridine calcium channel blockers has significant clinical implications. First, the increased plasma levels of the drugs may raise the incidence of adverse effects. Second, in hypertensive patients treated with dihydropyridines, sporadic concomitant ingestion of grapefruit juice may cause symptomatic hypotension. Third, the combination of a dihydropyridine antihypertensive with grapefruit juice can increase the therapeutic efficacy causing hypotension as has been illustrated in a published case report [22]. There are several other compounds (mainly polyphenols) in commonly eaten foods that inhibit CYP3A4. These include but are not limited to tannic acid (pomegranate), flavenoles (chocolate), and phenolic acid (coffee) and are also demonstrated in the following case discussion.

Case discussion

A 45-year-old obese male lawyer with a history of primary hypertension is followed in a nephrologist's office for CKD3b secondary to hypertensive nephro-arteriolar sclerosis. He also has other cardiovascular risk factors, including hypercholesterolemia and a BMI of $32\ \mathrm{kg/m^2}$.

Continued

You recommended several lifestyle changes that the patient has all implemented, including reduced calorie and fat intake and more exercise. The patient has taken up mountain biking which he does on most days.

On his most recent visit 2 weeks ago, he was feeling well. He had lost 3 kg of body weight during the preceding 6 weeks. His blood pressure was 119/76 mmHg with a heart rate of 72 bpm. The remainder of his physical examination was normal except for central obesity. The patient was stable on furosemide, 20 mg; atenolol, 50 mg; and enalapril, 20 mg daily. A complete blood count, Na, K, Cl, bicarbonate, calcium, and phosphorus serum levels were normal. Blood urea nitrogen (BUN) was 33 mg/dL, serum creatinine was 1.9 mg/dL, and LDL-cholesterol was 149 mg/dL. A dipstick urinalysis showed 1+ protein (30 mg/dL) but no blood. The patient was started on simvastatin, 40 mg nightly.

Now the nephrologist is called by the emergency room of the regional hospital to see the patient who had just been admitted for "total body pain." He did not have any accident. The pain started about 36 h ago suddenly after a strenuous mountain bike ride. He also noticed much reduced urine output and dark brown urine. On further questioning the patient reveals that he drank large amounts of orange juice during and after the bike ride. Physical findings were remarkable for severe pain upon palpation of both thighs, both upper arms and shoulders. Pertinent laboratory findings include K 6.1 mmol/L; BUN 41 mg/dL; creatinine 7.1 mg/dL; and creatine kinase activity (CK) 69,000 U/L; dipstick urinalysis shows strong blood and protein, and a urinary sediment is positive for brown granular casts but negative for blood cells. The ECG is normal except for signs of left cardiac hypertrophy.

The (obvious) diagnosis in this patient is oliguric acute kidney injury (AKI) secondary to rhabdomyolysis with severe hyperkalemia. The patient is started emergently on hemodialysis and simvastatin is discontinued. After 6 days of daily hemodialysis, his diuresis normalizes. The predialysis creatinine remains stable below 2.5 mg/dL and the pain disappears.

The cause of this patient's rhabdomyolysis is muscle injury from heavy exercise and simvastatin toxicity which, in turn, was caused by an increase in drug exposure from (transient) inhibition of CYP3A4 activity by compounds in the orange juice of which he drank large amounts during the bike ride. The patient should be advised to avoid orange, grapefruit, and citrus juices (except modest amounts) and he should be switched to either pravastatin or rosuvastatin both of which are not metabolized by CYP3A4.

St. John's wort, an over-the-counter herbal folk drug commonly used for mood elevation and as antidepressant, reduces the bioavailability of many drugs due to its induction of CYP3A4 activity in the liver and the

TABLE 50.5 Drugs that have greater efficacy with grapefruit (citrus) juice due to the inhibition of CYP3A4.

Antibiotics and antifungals	Most azoles Erythromycin Clarithromycin Telithromycin
Antihypertensives	Felodipine Nifedipine Nimodipine Nicardipine Isradipine Nisoldipine Verapamil
Immunosuppressants	Cyclosporine A Tacrolimus
Antihistamines	Astemizole
HIV-protease inhibitors	Saquinavir
Statins	Atorvastatin Lovastatin Simvastatin
Antianxiety drugs Antidepressants Sedatives	Buspirone Diazepam Midazolam Triazolam Zaleplon Carbamazepine Clomipramine Trazodone
Hepatitis C direct-acting antiretrovirals	Daclatasvir Simeprevir Telaprevir

small intestine (Table 50.6). Other compounds that also induce CYP3A4 include quercetin (broccoli, apples, red wine, onions, green tea, buckwheat flower, and tea; the latter has very high quercetin content; quercetin is also marketed as herbal remedy to "prolong life" and as antioxidant); capsaicin (the "hot" compound in chili pepper); flavone (celery, parsley); and genistein (fava beans, soy beans, and soy bean–derived processed foods) [16].

Nutrients and urinary excretion of drugs

The deficiency in some trace elements such as iron, zinc, copper, and selenium has been shown to influence the mixed function oxidase system in experimental animals, but for most such elements, studies in humans are not available. Moreover, even marked iron deficiency in man does not appear to affect oxidative drug metabolism.

In CKD the half-life of drugs that are primarily metabolized by hepatic glucuronidation may be prolonged [23].

TABLE 50.6 Drugs efficacy of which may be reduced by St. John's wort due to the induction of CYP3A4.

Antiretrovirals HIV	Indinavir Ritonavir Saquinavir Nelfinavir Nevirapine
Antiretrovirals hepatitis C	Daclatasvir Elbasvir/grazoprevir, glecaprevir/pibrentasvir, ledipasvir/sofosbuvir, ombitasvir/paritaprevir/ritonavir Simeprevir Sofosbuvir Sofosbuvir/velpatasvir Sofosbuvir/velpatasvir/voxilaprevir Telaprevir
Benzodiazepines	Alprazolam Midazolam
Immunosuppressants	Cyclosporine Tacrolimus Sirolimus (?)
Antiarrhythmics	Amiodarone Dronedarone Flecainide Mexiletine
Beta blockers	Propranolol Metoprolol Carvedilol
Calcium channel blockers	Verapamil Diltiazem Amlodipine Felodipine Nifedipine
Statins	Atorvastatin Lovastatin Simvastatin
Others	Digoxin Omeprazole Phenobarbital Warfarin Levodopa

There is circumstantial evidence that renal insufficiency per se reduces hepatic drug clearance. Although it is possible that fasting, malnutrition, or specific nutrient deficiencies may alter the hepatic glucuronidation of some drugs, the literature at present does not provide clearly supportive data.

The urinary excretion of certain drugs or of bioactive or toxic metabolites does not only depend on the degree of renal failure, that is, reduction in glomerular filtration rate (GFR) or creatinine clearance, but also on urinary pH. In patients with normal renal function and even in patients with moderate or even advanced CKD, urinary pH depends largely on dietary intakes, at least during the postabsorptive period.

A low-protein diet produces more alkaline urine, and conversely, a high-protein diet results in more acidic urine. Drugs or drug metabolites that are weak bases are more efficiently excreted in acidic urine, whereas more alkaline urine will promote the excretion of drugs or metabolites that are weak acids. Foods that potentially acidify the urine include meats, fish, eggs, cheese, bread, cranberries, plums, and prunes. More alkaline urine can be caused by milk, various fruits, and all vegetables except corn and lentils.

Interactions of food supplements with drugs

Patients with advanced CKD and those on maintenance dialysis are often prescribed food supplements, such as vitamins and iron preparations, or potassium and phosphate binders. Specific interactions between certain drugs and these food supplements have been described that may not only reduce the blood levels of the drug but may also reduce the drug efficacy. Thus it may be necessary to separate the timing of the intake of the food supplement from that of the drug. In general, the drug should be taken 1 hour before or 2 hours after the supplement, but in some circumstances this period of time should be even longer (up to 4 hours). For example, oral calcium salts reduce the intestinal absorption of levothyroxine by 30% or more when taken concomitantly or within 2 hours or less. It is recommended to keep 4 hours between the two medications.

Supplemental folic acid decreases the blood levels of phenobarbital [24] and may lead to breakthrough seizures. Pyridoxine (vitamin B_6) when given in large dosages (400 mg/d) can also reduce the serum levels of phenobarbital, possibly by increasing the activity of pyridoxal phosphate-dependent enzymes. In animal experiments, large doses of pyridoxine reduces the activity of isonicotinic acid against tuberculosis. Pyridoxine appears to form a Schiff base with isonicotinic acid which is then excreted in the urine or removed during dialysis. Concomitant therapy with pyridoxine and L-dopa in patients with Parkinson's disease reduces the efficacy of the latter drug and worsens the disease symptoms.

Excess intake of vitamin E can induce a hemorrhagic state in laboratory animals caused by vitamin K deficiency [25]. Patients on Coumadin therapy are at risk for developing hemorrhages that result from unwarranted further suppression of the vitamin K–dependent clotting factors by concomitant intake of vitamin E. It has been suggested that megadoses of vitamin C (>1 g/d) may lead to vitamin B_{12} deficiency apparently by the destruction of vitamin B_{12} by vitamin C when they are taken together.

Bioavailability of ciprofloxacin is reduced if the drug is coadministered with aluminum hydroxide-containing phosphate binders. Aluminum hydroxide as well as magnesium hydroxide reduce the bioavailability of ciprofloxacin by as much as 90% when given concomitantly or within <0.5 hours, and a lesser but still significant reduction occurs when the drug is given within up to 4 hours after the antacid. Similar reductions in the bioavailability occur for other fluoroquinolone antibiotics, such as norfloxacin, ofloxacin, and enoxacin when administered up to 4 hours after intake of aluminum-, magnesium-, or calcium-containing phosphate binders [26]. A significant decrease in the bioavailability of fluoroquinolones was also described by several authors to occur upon coadministration with several oral iron supplement preparations such as ferrous sulfate, fumarate, or gluconate. Calcium-containing phosphate binders or antacids have also been shown to reduce the bioavailability of tetracyclines [27]. Sevelamer does not appear to have such effects on drug bioavailability. The reduction of iron absorption from diet or ferrous sulfate due to coadministration of calcium-containing phosphate binders has been discussed earlier in this chapter.

Drug-induced nutritional deficiencies

Several prescribed or over-the-counter medicines reduce appetite and food intake. In patients with CKD or on maintenance dialysis, this may aggravate an already poor nutritional status and may contribute to frank malnutrition. However, of greater concern are more specific interactions of prescribed drugs with micronutrients, mainly with certain vitamins and minerals.

Drug-induced vitamin deficiencies

Vitamin metabolism and requirements in patients with renal disease and renal failure are described in Chapter 25, Vitamin D in Kidney Disease, and Chapter 26, Vitamin Metabolism and Requirements in Chronic Kidney Disease and Kidney Failure. Current guidelines do not recommend the routine prescription of micronutrient supplementation to patients with CKD1–5D albeit this does not preclude the need for vitamin supplementation in some patients [28]. Thiamine deficiency may be aggravated or caused by chronic alcoholism. The literature, at present, does not suggest that specific short- or long-term drug therapies may cause vitamin B_1 deficiency. However, thiamine deficiency may occur in severely ill patients who undergo parenteral nutrition [29]. Thiamine is a coenzyme for pyruvate dehydrogenase, and thiamine deficiency may cause the acute onset of unexplained, severe lactic acidosis [29]. Riboflavin deficiency can be caused or aggravated by long-term administration of chlorpromazine or amitriptyline. Pyridoxine deficiency may be caused by long-term treatment with isoniazid. It is recommended that vitamin B_6 supplements (10−15 mg/d) be prescribed for the entire period of time that isoniazid is taken. Vitamin B_6 deficiency may also be caused by hydralazine and penicillamine [15]. High doses of pyridoxine hydrochloride reduce the serum levels of anticonvulsants and may reduce the clinical seizure control. Chronic vitamin B_{12} deficiency may develop during long-term treatment with colchicine, metformin, or cimetidine, other H_2-blockers and proton pump inhibitors, especially if the dietary intake is marginal [30,31].

Several drugs antagonize folic acid and may cause megaloblastic anemia. These include phenytoin, phenobarbital, sulfasalazine, triamterene, trimethoprim, trimetrexate, and methotrexate [32]. On the other hand, folate supplementation may interact with these medicines and reduce their clinical efficacy. Daily dosages of folate of more than 5 mg reduce the plasma levels of phenytoin and phenobarbital and may reduce their therapeutic efficacy. A risk for the development of niacin deficiency may exist when treatment with isoniazid is prescribed. During such treatment, concurrent administration of niacin (100 mg/d) may be advisable. Retinoids and possibly retinol increase the blood cyclosporine levels [33]. Vitamin A supplements should be avoided in renal patients. In addition to Coumadin, there is a number of drugs that can cause vitamin K deficiency and that may induce or enhance severe bleeding. This has been described particularly with the administration of moxalactam, cefotetan, cefamandole, cefoperazone, and other cephalosporins that contain the methylthiotetrazole side chain. Vitamin K supplements should be administered concurrently with these antibiotics [34]. Weaker antivitamin K effects have been shown with tetracycline and cholestyramine. Ingestion of megadoses of vitamin E can cause vitamin K deficiency and should be avoided.

Drug-induced osteomalacia can be due to chronic intake of anticonvulsants, isoniazid and possibly cimetidine. Anticonvulsant therapy with phenytoin, phenobarbital, or carbamazepine results in reduced levels of 24,25-dihydroxyvitamin D_3, and this may play a role in the anticonvulsant-induced osteomalacia [35]. In patients with CKD, this drug-induced risk for osteomalacia may be additive to the increased risk of renal bone disease. Patients undergoing chronic dialysis therapy are often prescribed 1,25-dihydroxycholecalciferol or analogs. However, in patients with moderate CKD not receiving 1,25-dihydroxycholecalciferol, vitamin D supplements should be given concurrently with the previous drug treatments. Moreover, it is recommended to prescribe vitamin D supplementation (cholecalciferol or ergocalciferol) to maintain normal 25(OH)-vitamin D levels to patients with CKD1−5D [28].

Drug-induced mineral and trace element deficiencies

As a rule, the intakes of many minerals such as Na, K, Mg, Ca, and P correlate with the dietary protein intake [36]. Mineral and trace element deficiencies may develop due to poor nutritional intakes, and elderly patients are at greater risk. Mineral depletion can occur due to poor gastrointestinal absorption and/or enhanced renal excretion, the latter mainly in patients with lesser degrees of CKD. Both, reduced absorption and enhanced excretion of minerals can be caused by drug therapy. Potassium, calcium, magnesium, iron, and zinc are the most common minerals that become depleted in patients with CKD. Drug-induced potassium deficiency in patients with CKD most commonly results from diuretic therapy and can be caused by both thiazide and loop diuretics. With diuretic therapy, magnesium deficiency may also develop.

Concurrent intake of aminoglycosides and cephalosporin antibiotics can be interactive and cause potassium (and magnesium) depletion, particularly when intakes of these minerals are low which may occur with the ingestion of low-protein diets. Hypokalemia can also occur with gentamycin toxicity and during treatment with amphotericin B. Potassium deficiency may also be caused by laxative abuse with resulting potassium losses through the gastrointestinal tract. Lithium carbonate and levodopa can contribute to potassium deficiency [37]. Hypokalemia and potassium depletion worsen blood pressure levels in hypertensive patients and may contribute to the thiazide-induced carbohydrate intolerance.

Calcium deficiency can be caused by poor dietary intake, primary malabsorption or vitamin D-deficiency-induced malabsorption, or drug-induced hypercalciuria. Primary calcium malabsorption can result from enteropathy caused by neomycin, colchicine, methotrexate, and corticosteroids. Aluminum and magnesium hydroxide may reduce calcium absorption. Phenytoin and phenobarbital may interfere with vitamin D metabolism as described earlier. Loop diuretics, such as furosemide, torsemide, and ethacrynic acid, can cause hypocalcemia secondary to hypercalciuria. In patients with chronic renal failure, combined treatments with drugs that interfere with calcium metabolism are not uncommon.

Hypercalcemia in patients with CKD may result in soft tissue calcification and nephrocalcinosis that may contribute to the progression of renal disease or may itself cause CKD. The long-term combined intakes of large amounts of $CaCO_3$ and (vitamin D–fortified) milk can lead to severe chronic hypercalcemia and nephrocalcinosis causing CKD, the so-called milk-alkali syndrome [38]. Medullary nephrocalcinosis in this syndrome may also be the cause of CKD. In patients with CKD, hypercalcemia may result from the intake of calcium-containing phosphate binders and/or vitamin D derivatives.

Hyperoxalemia and hyperoxaluria can be caused or aggravated by vitamin C supplementation, even at moderate doses (i.e., 500 mg/d) [39]. Patients who eat relatively large amounts of foods that generate oxalate (e.g., green salads) and take moderate or megadoses of vitamin C have an increased risk to develop hyperoxalemia-associated complications [39].

Zinc deficiency may be caused or worsened by total parenteral nutrition without adequate zinc intake. Administration of penicillamine or corticosteroids has also been associated with zinc deficiency [40]. Zinc depletion causes or contributes to clinical symptoms that are often observed in patients with CKD, such as loss of appetite and altered taste and smell sensation. Loss of taste or smell may lead to reduced food intake and, hence, malnutrition. Aspirin (even at the low dose of 81 mg/d), ibuprofen, and other nonsteroidal antiinflammatory drugs may cause occult gastrointestinal bleeding and contribute to iron losses. Iron depletion and anemia may also be caused by poor food intake or reduced bioavailability from nonheme iron in foods such as due to concomitant calcium-containing phosphate binders. This has been discussed earlier. There are not sufficient data to indicate whether there are important drug interactions with other trace element micronutrients, such as selenium, molybdenum, chromium, manganese, rubidium, and others.

Nutrient interactions with some itemized drugs

Taurine and ACE-inhibitor effects

The amino acid taurine blocks actions of angiotensin II by inhibiting cellular Ca^{2+}-uptake and angiotensin II signaling. In experimental in vitro and in vivo studies, taurine food supplements were found to have renal antifibrogenic effects comparable to those of angiotensin converting enzyme (ACE) inhibitors [41].

Serum and red blood cell taurine levels tend to be lower in diabetics compared to normal subjects, and taurine food supplements can normalize taurine levels [42]. Foods rich in taurine include seafood, particularly crustaceans and molluscs, and lesser amounts are present in beef, pork, and lamb. Taurine-containing food supplements are available over the counter. Whether increased dietary taurine will indeed reduce the progression of renal disease and/or reduce the cardiovascular mortality in chronic dialysis patients is unknown due to the lack of respective clinical trials. Nevertheless, this may be an example of collaborative, beneficial drug–nutrient interaction.

Hyperuricemia and nontraditional uricosurics

Purine-rich diets can contribute to hyperuricemia. Asymptomatic hyperuricemia may cause CKD (uric acid nephropathy) or accelerate the rate of progression of CKD [43]. Whether asymptomatic hyperuricemia should be treated with uric acid–lowering agents is controversial [44]. In contrast, symptomatic hyperuricemia (gout, urate nephrolithiasis, urate or uric acid crystalluria, or known uric acid nephropathy) should be treated with uric acid–lowering drugs. Direct-acting uric acid–lowering drugs include allopurinol, febuxostat, and rasburicase. The latter is a human recombinant enzyme protein for intravenous administration and reserved for very severe hyperuricemia such as in the tumor lysis syndrome due to its high cost. In addition, canagliflozin, losartan, and fenofibrate also lower uric acid serum levels through uricosuric effects. It is conceivable that the treatment of patients with severe hyperuricemia with these latter drugs could cause crystalluric AKI but this complication has thus far not been reported. Diuretics, aspirin, cyclosporine A, mycophenolate mofetil, and ACE inhibitors raise serum uric acid levels [45].

Nutrient interactions with oral anticoagulants

Until recently, Coumadin was the mainstay of oral anticoagulation therapy in nonrenal as well as CKD patients. This drug is a prime example of the importance of foods that can interfere with drug actions. This is mainly because of the small therapeutic window between under- and overdose as well as its reduced efficacy by dietary vitamin K intakes. Table 50.7 summarizes commonly consumed foods with relatively high vitamin K content. In contrast the intake of large amounts of vitamin E can cause vitamin K deficiency and increase the bleeding risk in patients taking Coumadin. In addition to several blood coagulation enzymes, some other proteins require vitamin K as a cofactor for their activation by carboxylation. These include proteins with functions in bone and calcium metabolism such as osteocalcin and matrix Gla protein [47]. Hence, warfarin is also a risk factor for osteoporosis and vascular calcifications in ESRD patients.

TABLE 50.7 Common foods with high-phylloquinone (vitamin K_1) content [46].

Phylloquinone (μg/100 g)	
Vegetables	
Collard greens	440
Spinach	380
Salad greens	315
Broccoli	180
Brussels sprouts	177
Cabbage	140
Bibb lettuce	122
Asparagus	60
Okra	40
Vegetable oils	
Soybean oil	193
Canola oil	127
Cottonseed oil	60
Olive oil	55

Several novel orally effective small molecule factor Xa or thrombin enzyme inhibitor anticoagulants have recently been approved by regulatory agencies (rivaroxaban, dabigatran, apixaban, edoxaban, and betrixaban). The FDA has approved their usage in patients with CKD stages 1–4 (specifically CrCl ≥ 15 mL/minute as estimated with the Cockcroft–Gault formula). Moreover, apixaban and rivaroxaban have also FDA-approved dosing recommendations in hemodialysis patients. The EMA does not recommend the use of these drugs in dialysis patients [47]. High-fat, high-calorie diets tend to reduce the rate of absorption of dabigatran but overall drug availability is not substantially different from fasting [48]. Similar food interactions were shown for rivaroxaban [49]. Other important food interactions have not yet emerged. Since these drugs are in clinical use for only a relatively short period of time, other drug–nutrient interactions may come to attention.

Apixaban, edoxaban, and rivaroxaban are mainly metabolized through CYP3A4 [50]. Thus nutrients and food supplements that induce CYP3A4 such as St. John's wort might reduce drug levels and anticoagulant efficacy (Table 50.6). Overanticoagulation could occur with large amounts of citrus juice intake due to CYP3A4 inhibition (Table 50.5). Thus far, cases with either nutrient-dependent interaction have not been reported. For this reason, these drugs are not included in Tables 50.5 and 50.6. Betrixaban and dabigatran are not metabolized by CYP450 enzymes.

Interactions of calcineurin inhibitors with nutrients

Treatments with cyclosporine A or tacrolimus continue to be part of immunosuppressive regimens that are used in kidney transplantation. Cyclosporine has several side effects that include nephrotoxicity, hepatotoxicity, hypertrichosis, gingival hyperplasia and hyperuricemia, and gout (7% of patients); the latter particularly when used together with loop diuretics. Cyclosporine is incompletely absorbed from the gastrointestinal tract, and the administration of the drug with foods tends to increase absorption. The incomplete absorption of intact cyclosporine is, in part, caused by metabolism in the small bowel wall [51]. Cyclosporine is metabolized by oxidation in liver microsomes through the CYP3A4 isoenzyme system. This enzyme system is also expressed in the small bowel wall which explains the first-pass metabolism of cyclosporine A. See also Tables 50.5 and 50.6.

Cyclosporine A is a highly lipid-soluble drug, and about 40% of cyclosporine in plasma is bound to lipoproteins. Thus it is reasonable to speculate that dietary fat intakes or the fat content of meals may raise the gastrointestinal absorption and plasma levels of cyclosporine A, but this has not been confirmed in clinical trials.

As indicated earlier, citrus juices, particularly grapefruit juice, reduce the metabolic rate of cyclosporine and raise its blood levels, possibly through the inhibitory effects of flavonoids and other compounds on CYP3A4 enzyme. The inhibition of CYP3A4 by grapefruit juice and other citrus juices and fruits raises the area-under-the-curve and causes an increase in 24 hours trough cyclosporine level (Table 50.5) [52]. St. John's wort and caspofungin induces CYP3A4 activity (Table 50.6). Both cyclosporine and tacrolimus can cause a number of metabolic complications, including phosphorous, magnesium or potassium depletion, hyperkalemia, glucose intolerance and diabetes mellitus, and hyperlipoproteinemia. Tacrolimus is mainly metabolized through CYP3A enzymes. Hence, food/food supplement interactions can affect tacrolimus blood levels: St. John's wort induces CYP3A and may decrease tacrolimus blood levels. Grapefruit juice that blocks this enzyme system increases blood levels (Tables 50.5 and 50.6). Drug inhibitors of CYP3A (calcium channel blockers, caspofungin, and azoles) can increase tacrolimus levels.

Absorption of tacrolimus from the gastrointestinal tract is substantially influenced by food: absorption is greatest with fasting. High-fat diets reduce tacrolimus absorption and drug availability more than high-carbohydrate diets [53].

Nutrient interactions with potassium binders

Sodium polystyrene sulfonate (SPS), patiromer, and sodium zirconium cyclosilicate (ZS-9) are cation-exchange compounds with either sodium (SPS, ZS-9) or calcium as counterion. SPS and patiromer are polymer resins, whereas ZS-9 is an inorganic silicate. As such, these compounds will bind other minerals than potassium in the gastrointestinal tract. Hypomagnesemia has been reported most commonly with patiromer compared to the other two binders [54]. The binding of nonpotassium cations can cause nutritional deficiencies and competitively reduces the efficacy of the binder to improve hyperkalemia. ZS-9 binds mainly protons in addition to potassium and increases the gastric pH which is thought to affect pH-dependent solubility of some other drugs.

The FDA-approved package insert for patiromer requires to take the drug with food. However, a recent clinical study demonstrated equal efficacy and tolerability if this potassium binder is taken with or without food [55].

Nutrient interactions with phosphorus binders

Hyperphosphatemia worsens with progressing renal disease and is common and can be severe in hemodialysis patients. High serum phosphorus levels are causative in renal bone disease, as well as soft tissue, arteriolar (calciphylaxis), and vascular calcifications. High phosphate–containing foods include cheeses, dairy products, meats, and coca cola. As a rule, high protein intakes are associated with large dietary phosphate loads. Many processed foods contain phosphate compounds as stabilizers and preservatives.

Aluminum hydroxide is largely abandoned for chronic use as phosphate binder due to aluminum absorption and deposition in brain and bone causing dementia and bone disease. Magnesium-containing compounds are also not commonly used due to their risk of hypermagnesemia. Calcium-containing phosphate binders ($CaCO_3$, Ca-acetate) can increase calcium intakes above recommended amounts (800–1000 mg in CKD1–4 [28]) and appear to contribute to vascular calcifications [56,57]. Newer (calcium-free) phosphate binders include sevelamer (hydrochloride or carbonate), lanthanum carbonate, sucroferric oxyhydroxide, and ferric citrate.

In addition to phosphate, sevelamer also binds fat-soluble vitamins (vitamin D/calcitriol, E, K, and folic acid). This effect of sevelamer is not shared by lanthanum carbonate or sucroferric oxyhydroxide [58,59].

Iron-based phosphate binders, sucroferric oxyhydroxide, and ferric citrate were thought to have added benefits of supplying iron to patients with renal disease who often have iron deficiency. This did not materialize with sucroferric oxyhydroxide in clinical trials but ferric citrate improves transferrin saturation and hemoglobin in dialysis and predialysis patients [60]. With ferric citrate, there is a moderate risk of iron overload in anuric dialysis patients, and monitoring of ferritin and transferrin is advised [60]. The citrate content of the latter drug can raise dietary aluminum absorption [60]. However, the aluminum serum levels increase only minimally and it is very doubtful that aluminum toxicity can arise solely from aluminum in foods.

Novel phosphate-lowering drugs that block the sodium-dependent phosphate cotransporter NpT2b or the sodium hydrogen exchanger-3 (NHE-3) in the intestine, namely, nicotinamide and tenapanor, respectively, are currently in clinical development [60–62]. Nicotinamide, a form of vitamin B_3, is present in foods and food supplements. At pharmacological dosing (0.5–2 g/d), it reduces serum phosphate levels in hemodialysis patients similar to sevelamer [62]. Of concern is the systemic accumulation of the potentially toxic metabolite 2PY [62]. Tenapanor is a minimally absorbed small molecule direct inhibitor of the gastrointestinal NHE-3 [61,63]. It inhibits intestinal Na absorption, raises stool Na, and reduces urinary Na excretion [63]. The mechanism by which inhibition of NHE-3 reduces phosphate absorption is unclear but may involve indirect NpT2b inhibition. Tenapanor commonly causes diarrhea at high doses in a 4-week clinical trial [61], longer clinical studies are currently being performed. In normal subjects, stool phosphate excretion is greater if tenapanor is taken with food (before or after a meal) rather than in a fasting state [63]. Other drug–nutrient interactions with tenapanor are not known but clinical (trial) experience is minimal.

Oral hepatitis C therapy and nutrient interactions

Hepatitis C is not uncommon in patients with CKD or those on chronic dialysis or in renal transplant patients. The introduction of direct-acting antiretroviral nucleotide and protease inhibitors has revolutionized the management and cure of patients with hepatitis C. These drugs are commonly used as single pill, fixed dose combinations of two or even three antiretrovirals, including novel combinations with pan-genotypic efficacy of $\geq 96\%$ in the patients with normal renal function [64]. There is very little information about drug–nutrient interactions with these direct-acting hepatitis C antiretrovirals in general and in renal disease patients specifically. Almost all hepatitis C protease and nuclease inhibitors are CYP3A4 dependently metabolized and, hence, their antiviral efficacy is reduced by St. John's wort (Table 50.6) [20]; daclatasvir, simeprevir, and telaprevir are known to be affected by citrus (grapefruit) juice (Table 50.5).

Nutritional implications of excipients in drugs

Excipients are therapeutically inactive additives in drug preparations that serve as solvents, solubilizers, or stabilizers. Most commonly, these compounds are inert. However, in some drug preparations excipients have substantial desirable or undesirable nutritional or metabolic effects [65].

Amprenavir (Agenerase, GlaxoSmithKline PLC, Brentford, Middlesex, United Kingdom), an HIV-protease inhibitor that is not marketed anymore in the United States, contained multiple excipients in its capsule or oral solution preparations, including vitamin E and propylene glycol. At therapeutic dosing the daily administered vitamin E amount was 1744 IU/d, or about 80-fold the recommended daily allowance and above the level considered toxic [66]. With the oral solution the propylene glycol intake (about 1.6 g/kg BW/d) could cause severe high anion-gap lactic acidosis in vulnerable patients (young children, pregnant women, hepatic insufficiency, renal failure, patients taking disulfiram, or metronidazole).

The ACE-inhibitor quinapril (Accupril, Pfizer, New York, NY) contains dose dependently up to 400 mg of magnesium which will be additive to the dietary intake of this mineral and may cause hypermagnesemia.

Polycarbophil (FiberLax, FiberCon, and other brand names) is an over-the-counter bulk-forming laxative that contains large amounts of Ca^{2+}. Each 625-mg tablet contains 140-mg Ca^{2+} and daily intakes at the recommended dose may exceed 1 g of calcium.

Propofol is poorly soluble in water and preparations contain 10% soybean oil to form an oil-in-water emulsion (causing the milky appearance of the intravenous preparation). Depending on dosing, the daily energy provision may exceed 1000–1500 kcal when propofol is administered as a continuous intravenous infusion in the intensive care units.

Other excipients include lactose (possibly symptomatic in patients with lactose intolerance), peanut oil (present in oral progesterone preparations and some valproic acid capsules; may cause severe allergic reactions in patients with peanut allergy), gluten (severe reactions in patients with celiac disease), and some chemical dyes such as tartrazine (FD&C Yellow No 5) which can cause severe complications especially in patients with aspirin hypersensitivity.

Enteral tube feeding and oral drug administration

Enteral tube feeding may be a necessary or desirable mode of nutrient delivery in some patients with CKD or ESRD either transiently during periods of acute, severe illness or for longer periods of time. In such patients, drugs may be administered preferably by intravenous routes, but enteral drug administration sometimes may be necessary, since many medicine preparations are not available for intravenous infusion.

Several considerations should be taken into account when giving oral drug preparations through enteral feeding tubes. First, oral medicines should be delivered into the stomach to ensure proper preparation for subsequent drug absorption in the jejunum. Second, drugs should be used in liquid form rather than as crushed tablets. Third, slow-release or enteric-coated tablets should not be crushed at all. Fourth, drugs may not be compatible with the tube feeding formula and should not be mixed with formula. Thus tubes should be flushed with water before and after drug administration. Fifth, the osmolality of some liquid drug preparations may be very high and may add to the osmolality of the formula. A complete list of commercially available liquid preparations of commonly used drugs has been published elsewhere [67,68].

Only few studies have examined the bioavailability of drugs when administered with enteral formulas, and this information is not available for most medicines. Effervescent potassium tablet preparations cause marked coagulation of the enteral formula, whereas potassium chloride or gluconate solutions are compatible [69]. Administration of aluminum-containing phosphate binders with some enteral formulas can lead to precipitation of formula proteins with the aluminum salts and gastrointestinal plug formation can occur. Case reports have suggested that enteral tube feeding causes resistance to warfarin. Apparently, this results from the antagonistic effect of vitamin K that is present in enteral formulas. In patients undergoing treatment with warfarin, a formula with a lesser vitamin K content should be used and will improve the response to the anticoagulant. There is also evidence that warfarin may directly bind to the feeding tube reducing drug availability [70]. Some drug compounds are light sensitive and inactivated by light exposure and preparation, and tube administration should be performed in the dark (nifedipine, nicardipine, metronidazole, amiodarone, and furosemide) [67].

Little is known about interactions of many other drugs that may be used in patients with renal failure undergoing tube feeding. Hence, close monitoring of the plasma drug levels, treatment response, and compatibility with the formula are necessary.

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PART VIII

Prevention of frailty and improvement of physical performance

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CHAPTER

51

Exercise training for individuals with advanced chronic kidney disease

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Introduction

Individuals with advanced chronic kidney disease (CKD) exhibit malaise and significantly reduced capacity for virtually any form of exercise apart from self-care. These patients are commonly severely deconditioned, exhibit significant skeletal muscle weakness, and have abnormal muscle morphology, all of which lead to diminished physical performance, reduced quality of life, and increased mortality. For patients undergoing chronic dialysis, mortality is significantly related to the optimal dialysis dose [1], age, race, heart failure, physical functioning, and comorbidity scores [2]. In nondialyzed CKD patients, survival correlates with higher physical function and greater physical activity [3,4]. Of these predictive factors, only physical functioning and physical activity can be easily and directly improved. As illustrated in Fig. 51.1, sedentary behavior, which is especially prevalent in advanced CKD, is thought to directly effect a number of comorbidities, including inflammation, oxidative stress, and survival, although proof of a direct causal relationship between sedentary behavior and these disorders is lacking.

Exercise training has mitigated these negative effects in healthy individuals, and a growing body of evidence suggests similar outcomes in people with CKD. As with the general population, regular exercise training (planned, structured, repetitive, and purposeful in improving or maintaining physical fitness) [5] and increased physical activity (any bodily movement that results in energy expenditure) result in substantial benefits for persons with CKD.

Exercise programs for individuals with advanced CKD were introduced over 40 years ago [6]. Since then, a substantial body of evidence in support of exercise therapy in CKD has evolved through randomized controlled trials (RCT), systematic reviews, and metaanalyses [7–12]. Despite this evidence, renal rehabilitation programs have been neglected and lag far behind those for cardiac [13,14] and pulmonary [15,16] rehabilitation programs. Evidence-based guidelines for exercise training are also available for individuals with CKD [17,18]. These offer evidence-based guidance based on analyses of over 15 years of randomized, controlled trials of exercise training in people with CKD. The majority of exercise training outcomes and recommendations have been gathered from individuals with advanced kidney disease receiving dialysis, but the general approach to exercise training is applicable to individuals with CKD stages 1–5 [8,17,18]. There are no specific guidelines for exercise training in renal transplant patients.

This chapter provides nephrologists and the renal care team with a review of basic principles underlying exercise training, methods for assessing efficacy outcomes, and the variables used in exercise training program design. These are meant to provide the necessary background and guidance for exercise programming for patients with advanced CKD for whom exercise is beneficial. Additional resources for this purpose are provided at the end of this chapter. Finally, a renewed call to action is proposed for physicians and the renal care team to be more engaged with patients regarding exercise, emphasizing the value of regular physical activity and ensuring that exercise is part of the treatment plan.

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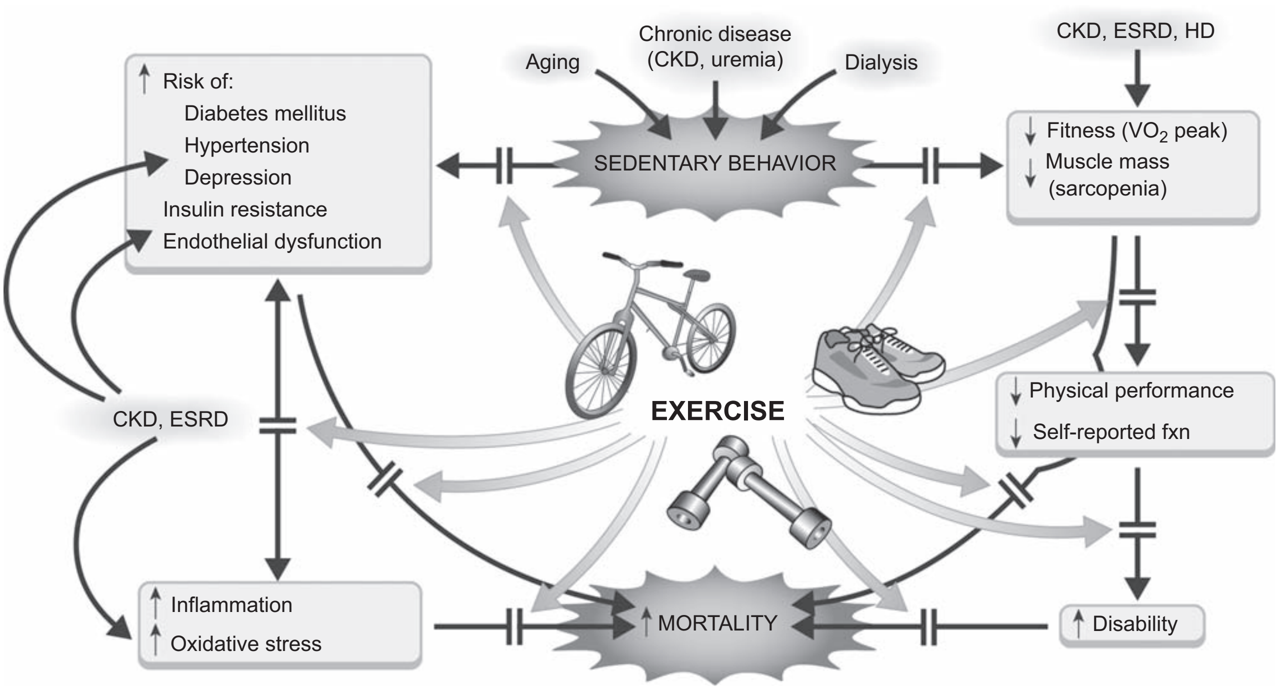
Chronic disease
(CKD, uremia)
Aging
Dialysis
CKD, ESRD, HD
↑ Risk of:
Diabetes mellitus
Hypertension
Depression
Insulin resistance
Endothelial dysfunction
SEDENTARY BEHAVIOR
↓ Fitness (VO_2 peak)
↓ Muscle mass
(sarcopenia)
CKD, ESRD
EXERCISE
↓ Physical performance
↓ Self-reported fxn
↑ Inflammation
↑ Oxidative stress
↑ MORTALITY
↑ Disability

FIGURE 51.1 Potential adverse effects of sedentary behavior and chronic kidney disease and potential beneficial effects of exercise intrvntions. *CKD*, Chronic kidney disease; *ESRD*, end-stage renal disease; fxn, function; *HD*, hemodialysis. Source *From Johansen KL. Exercise in the end-stage renal disease population. J. Am Soc Nephrol 2007; 18:1845–1854.*

Impaired physical capability of advanced CKD patients

Individuals with advanced CKD commonly are severely deconditioned, inactive and have low tolerance for any physical activity beyond self-care [19–21]. The Dialysis Outcomes and Practice Patterns Study conducted in 12 countries with nearly 21,000 maintenance hemodialysis (MHD) patients reported that over half the sample acknowledged some type of exercise <1 day/week or never [22]. See Fig. 51.2.

Malaise, significant skeletal muscle weakness [23–26], and abnormal muscle morphology [27,28] are common characteristics of patients with advanced CKD. The cause of weakness is not entirely understood, but muscle atrophy, myopathy, deconditioning, malnutrition, and carnitine deficiency have been proposed as contributors [24,26]. Peak oxygen uptake ($\dot{V}O_2$ peak), strength, and physical function levels in patients with end-stage renal disease (ESRD) are approximately 60%–70% of age-matched healthy individuals, even with the use of erythropoietin stimulating agents [25,27,29,30]. This low functional capacity contributes to low exercise tolerance, and poor physical functioning, anxiety, depression, and loss of sleep in patients with ESRD [31–33]. In a national study of over 2400 new dialysis patients, 75% described severe limitations in vigorous activities, and 42% of patients acknowledged severe limitations in moderate activities such as moving a table or vacuuming [34]. Dialysis patients have significantly greater muscle atrophy in contractile areas compared with healthy controls, even when corrected for habitual activity level. The muscle atrophy is proportional to muscle weakness and reduced physical performance, as determined by gait speed [25]. In addition,

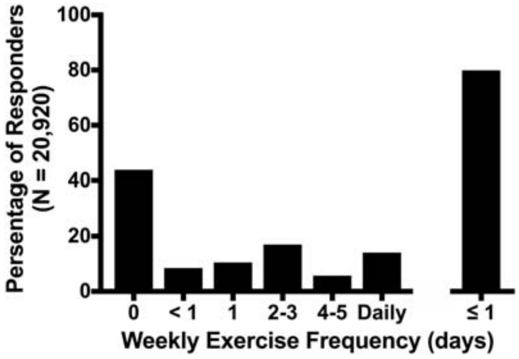

FIGURE 51.2 Number of days of exercise self-reported by 20,920 individuals with end-stage renal disease out of 22526 participants from 12 countries in the Dialysis Outcomes and Practice Patterns Study. Source: *Adapted from Tentori F, Elder SJ, Thumma J, Pisoni RL, Bommer J, Fissell RB, et al. Physical exercise among participants in the Dialysis Outcomes and Practice Patterns Study (DOPPS): correlates and associated outcomes. Nephrol Dial Transplant 2010;25:3050–62. https://doi.org/10.1093/ndt/gfq138. Correspondence and offprint requests to Francesca Tentori; e-mail: francesca.tentori@arborresearch.org. © The Author 2010. Published by Oxford University Press on behalf of ERA-EDTA. All rights reserved. For Permissions, please e-mail: journals.permissions@oxfordjournals.org.*

the limitation in peak oxygen uptake ($\dot{V}O_2$ peak), the highest oxygen uptake achieved during an incremental exercise test and an indicator of functional capacity, may be due, in part, to impaired skeletal muscle function. However, this impaired skeletal muscle function may be improved with exercise training with consequent improvements in $\dot{V}O_2$ peak.

Excitation–contraction coupling, central activation, and specific tension, when the latter is expressed as the ratio of maximal voluntary strength to contractile cross-sectional area (CSA), are not different between MHD patients and controls [24,27]. This suggests that muscle atrophy is a major cause of muscle weakness and the ensuing decrements in physical function. More than 60% of MHD patients are over age 65 and are sarcopenic [35]. Loss of edema-free lean mass in MHD patients, whether as a consequence of a chronic catabolic state, uremic myopathy, or decreased levels of androgens, growth hormone, and/or the insulin-like growth factor (IGF) system, is a common observation [36]. Comorbid conditions, including diabetes mellitus, obesity, heart failure, vasculitis, and other inflammatory diseases, may play an important contributory role. In addition to the myriad functional limitations experienced by those with CKD, the loss of edema-free lean body mass (LBM) common to this population may portend increased risk of mortality [37]. The Dialysis Morbidity and Mortality Study reports that mortality risks, expressed as relative risk (RR), were greatest in patients with ESRD who had severe limitations in moderate (RR, 1.72) or vigorous (RR, 1.51) physical activity when compared with those with minimal or no limitations. For MHD patients who exercised two to three or four to five times/week, mortality risks were substantially lower, RR = 0.74 and RR = 0.70, respectively [38]. It is eminently clear that individuals receiving MHD have an important need for interventions that mitigate the effects of ESRD on physical function and possibly morbidity, and mortality and that may reduce risks due to comorbidities, especially cardiovascular disease (CVD). Interventions that result in improved physical function would be welcome in the ESRD population. Well-applied and regularly practiced exercise training and increased physical activity is just such as intervention. Data collected for over 40 years in this area have demonstrated significant physical performance and health-related benefits in those MHD patients who reasonably comply with exercise training guidelines. Many of these benefits are presented next.

Demonstrated value of exercise and physical activity for people with CKD

In the general population, lifestyle change, including physical activity and exercise training, are listed among the highest priorities for improving health and reducing chronic disease risk. [39,40] Insufficient exercise and physical activity are well-known risk factors for many chronic diseases [41]. This is certainly true for the CKD population as the debilitating effects of CKD lead to the downward spiral of increased physical inactivity and increased comorbidity risk, especially that of CVD and increased mortality [42]. The National Kidney Foundation KDOQI Clinical Practice Guidelines recommend lifestyle issues, including physical activity, as a cornerstone therapy often with profound impact on patients receiving MHD [43]. Eight systematic reviews, some with metaanalyses, of exercise training effects in CKD have been reported in the last 9 years [4,7–12,44]; a summary of the effects of endurance (aerobic) training (AT), progressive resistance training (PRT), and combined aerobic and resistance training (CT) from these reports are presented in Table 51.1.

As indicated in Table 51.1, most data have been gathered from individuals undergoing MHD and provide an evidence base for the value of exercise training in advanced CKD. Clearly, more work is needed with nondialyzed CKD patients and renal transplant patients.

Over 40 years ago, Jette and colleagues reported a case study that investigated the feasibility of administering exercise training to a patient receiving MHD [45]. The twice-weekly exercise program conducted on nondialysis days was associated with improved functional capacity, improved mood, and decreased blood phosphorus levels. Patricia Painter, a research pioneer in the application of exercise training with MHD patients, investigated the effects of 6 months of thrice-weekly cycle exercise with the duration progressing up to 30 continuous minutes during the second or third hour of dialysis [31]. After 6 months a significant 23% improvement in $\dot{V}O_2$ peak was reported with no change in the control group. Compliance in the training group was 91%. This study was the first to show that significant benefits could be achieved by regularly performing simple cycling exercise during the hemodialysis (HD) procedure. Now 33 years later, this seminal work has been confirmed many times, not only showing benefits for aerobic capacity but also for several other health- and performance-related variables (Table 51.1).

Aerobic capacity, $\dot{V}O_2$ peak, that is, the maximum rate of oxygen consumption determined by progressively increasing work rate, is recognized as the best noninvasive parameter for assessing the integrated function of the cardiopulmonary and muscular systems [46–48]. Consequently, $\dot{V}O_2$ peak has been studied extensively in MHD patients, and consistently increased $\dot{V}O_2$ peak with exercise training has been

TABLE 51.1 Summary of eight systematic reviews reporting outcomes from aerobic training (AT), progressive resistance training (PRT), and combined (AT + PRT) training in nondialyzed chronic kidney disease patients [nandrolone decanoate (ND)], maintenance hemodialysis (MHD) patients, and kidney transplant recipients (TR).

		Change with exercise training[a]											
		Any			AT			PRT			AT + PRT		
	Variable	ND	MHD	TR	ND	MHD	TR	ND	MHD	TR	ND	MHD	TR
Cardiovascular and aerobic performance	$\dot{V}O_2$ peak	1	1	1	1, 2	1, 2, 3, 5, 6	1, 2		1			1, 5 6,	
	SBP at rest	1–	1< >, 6< >	1< >	1	1< >, 5< >	1< >,					1–, 5–	
	DBP at rest	1< >	1< >, 6< >	1< >,	1< >	1< >, 5< >	1< >					1< >5	
	HR at rest												
	HRmax												
	LVMi		1< >									1< >	
Musculoskeletal	Muscle strength	1	1, 7	1< >		1, 7gs	1< >	1, 4	17			1, 7< >	
	Type I fiber area												
	Midthigh muscle area	1	1			1		1, 4	1			1	
	Thigh muscle attenuation												
Physical performance	Sit-to-stand		7			7							
	Gait speed												
	Stair climb												
	Walking capacity	1< >	1< >, 7, 6,		2< >	1< >, 2. 3< >. 7, 6			1< >		1< >	1< >, 7< >	
Body composition	Body mass												
	Lean body mass		7			7			7				
	Fat mass												
	Leg mass		7			7< >		4	7				
	Circumferences												
Hemoglobin						3							
Albumin						3< >							
Depression						3							
eGFR					2< >		2< >						
Kt/V						2, 5, 6< >, 8< >			5< >			5< >	
Phosphate removal						8							
HR-QOL			1 6			1< >, 2, 3	2< >	4			1		
Mortality						2< >							

1 = Heiwe and Jacobson [8]; 2 = Yamagata et al. [44]; 3 = Chung [239]; 4 = Cheema et al. [9]; 5 = Scapini et al. [10]; 6 = Huang et al. [11]; 7 = Lu et al. [12]; 8 = MacKinnon et al. [4]. *DBP*, Diastolic blood pressure; *eGFR*, estimated glomerular filtration rate; *gs*, grip strength; *HR*, heart rate; *HR-QOL*, health-related quality of life; *LVMi*, left ventricular mass index; *SBP*, systolic blood pressure.

[a] *Numbers alone correspond with sources and indicate significant improvement relative to controls. Numbers with <>; for example, 1< > indicates no difference in outcome between treatment and control.*

well documented [7,8,10–12,30,49,50]. The overall improvement in $\dot{V}O_2$ peak in CKD patients (mostly those receiving MHD) who had undergone exercise training in these studies was about 23% or 4.3 mL/kg/min/min. This represents a 1.2-MET increase, where 1 MET is equivalent to the resting metabolic rate expressed as an oxygen uptake of 3.5 mL/kg/min. Although seemingly small, the 1.2-MET improvement in $\dot{V}O_2$ peak may bring about important benefits. Evidence is now available that indicates that higher intensity exercise yields a better result and that combined aerobic exercise training and RT yields larger improvements in $\dot{V}O_2$ peak than aerobic training alone [10].

Aerobic capacity is an independent predictor of mortality, has high prognostic ability, and outperforms traditional risk factors and other exercise test responses (including markers of ischemia) for predicting outcomes in people with and without CVD, patients with chronic heart failure (CHF), hypertension, diabetes, or obesity [51–60], even when estimated from treadmill time rather than from direct measurement [61]. Several studies have now shown in people without CKD that increasing aerobic capacity, especially in those with very low fitness, for example, a $\dot{V}O_2$ peak <5–6 METs with maximal exercise (i.e., $\dot{V}O_2$ peak of 17.5–21 mL/kg/min) has a significant impact on reducing cardiovascular and all-cause mortality. In people without CKD, improving from this low fitness category, which is approximately the fitness level of MHD patients, every 1-MET increase in $\dot{V}O_2$ peak reduces mortality risk by 10%–25% [62,63]. In 2011 Aspenes et al. studied the association between $\dot{V}O_2$ peak and cardiovascular risk factors in 4631 apparently healthy Norwegian men and women [52]. In this cohort, every 5-mL/kg/min decrease in peak $\dot{V}O_2$ was associated with a 56% higher odds of cardiovascular risk clustering. Inasmuch as many MHD patients often have some form of intercurrent CVD accounting for approximately 30% of their morbidity and mortality [64], improved their $\dot{V}O_2$ peak should provide a significant benefit. In addition, increasing one's capacity for work decreases the relative percentage of that capacity that is required to perform at more common submaximal levels of functioning. Hence, exercise training regimens designed to improve aerobic capacity should be of significant benefit to patients with CKD and should be recommended and available to all.

Less is known about the prognostic ability of $\dot{V}O_2$ peak in MHD patients. Sietsema studied 175 MHD patients who had completed cardiopulmonary exercise testing (CPXT) with measurement of $\dot{V}O_2$ peak to determine its value in predicting survival [65]. There were 23 deaths during the 39-month follow-up period with 19 deaths in subjects who were below the median $\dot{V}O_2$ peak of 17.5 kg/min and four deaths in the subjects who were above the median, ($P = .009$). $\dot{V}O_2$ peak proved to be a better predictor of mortality than other traditional predictor variables. Although this was a retrospective study with a relatively small number of deaths, it supports the contention that increasing $\dot{V}O_2$ peak through properly administered doses of regular exercise training in the MHD population might increase survival. Less is known about the association between improved $\dot{V}O_2$ peak and mortality in nondialyzed CKD patients and chronic peritoneal dialysis (CPD) patients. However, trials conducted in nondialyzed advanced CKD patients suggest that appropriate exercise training can increase aerobic capacity and protect against the decline in cardiac function and progression of CVD through modification of risk factors [66]. More research that examines the causal nature of these relationships is needed, particularly in the predialysis CKD stages.

Loss of muscle mass, increased muscle weakness, and diminished physical performance are common in advanced CKD patients. Left unchecked, further muscle dysfunction and sarcopenia may ensue that lead to further weakness, loss of physical function, and progressively reduced quality of life and increased mortality. The most potent exercise countermeasure for these debilitating changes is PRT. PRT has not received the same attention as a training modality in CKD as aerobic training. However, in healthy individuals, adaptations to systematically applied PRT include increased LBM, skeletal muscle mass and fiber hypertrophy, improved muscle strength, power, and fatigability and improved physical performance. These changes have been reported for both men and women of all ages [67,68], including nonagenarian men [69]. Likewise, significant increases in muscle performance and LBM have been reported after PRT in patients with CVD [70], diabetes mellitus [71,72], Chronic obstructive pulmonary disease (COPD) [73,74], and those with HIV infection [75]. Based on these observations in healthy individuals and in patients with some chronic diseases, several studies have investigated the anabolic effects of PRT in CKD patients.

In the first study of resistance exercise training conducted during MHD, Johansen and colleagues compared changes in LBM and muscle size resulting from resistance exercise training, weekly injections of nandrolone decanoate (ND), or both interventions in a 2 × 2 factorial design [76]. A total of 12 weeks of PRT alone did not prove to be an adequate stimulus for increasing LBM, but quadriceps muscle CSA increased significantly. Conversely, subjects randomized to receive ND experienced greater gains in these measures and the effects were additive in subjects receiving both ND and PRT (please see Chapter 52: Anabolic and anticatabolic agents in kidney disease and kidney failure).

Kopple and colleagues compared anabolic responsiveness in ESRD subjects randomized to 21 weeks of AT, PRT, combined AT plus PRT (CT), or nonexercising controls [77]. Importantly, total work done by subjects in the CT group was equal to both 50% of the endurance training (ET) group and 50% of the resistance training (RT) group. Changes in transcriptional levels of several growth factors in the right vastus lateralis muscle were used to examine the anabolic response to these modes of training. The subjects randomized to PRT alone exhibited no change in fat-free mass, determined by dual X-ray computerized tomography as well as no significant changes in several mRNA growth factors in the skeletal muscle other than increased levels of IGF-IEa mRNA. The mRNAs for IGF-IEa, IGF-IEc, and IGF-II each increased significantly in the CT group. There was a not-statistically significant trend in each of the three exercise training groups toward increased mRNA expression for most other growth factors. Myostatin mRNA decreased by 23% in the PRT group, but this change was not significant. The authors identified several factors that might have influenced these results, including the severe deconditioning and comorbidities of the patients in all groups, an inadequate training stimulus for the PRT group or the possibility of myopathies that might have impaired training responses. The lack of statistical significance in the foregoing changes might have been due to the small number of subjects in each group. When all three groups of the MHD patients who underwent exercise training were pooled, muscle transcriptional levels for other growth factors increased significantly, and the mRNA for myostatin decreased significantly.

An Australian group initially randomized 49 MHD patients to 12 weeks of intradialytic PRT or a no-exercise control to examine markers of muscle performance, physical function, body composition, and associated variables [78]. After interim measurements at 12 weeks, the trained subjects continued training for an additional 12 weeks, whereas the control group crossed over to the same PRT program as the original exercise group. The primary outcome variables were midthigh CSA and thigh muscle attenuation, an indicator of intramuscular lipid accumulation. After the first 12-week phase of the study, no significant improvement in thigh CSA was seen in either group. Thigh muscle attenuation decreased by 1.2% ($P>.05$) in the PRT group reflecting a trend toward less muscle lipid content and therefore better muscle quality. This change was significantly different than the 0.34% increase in thigh muscle attenuation in the control group. At 24 weeks the change in thigh muscle CSA was significantly greater in the group that had trained for 24 weeks versus the crossover group who had completed just 12 weeks of training. There was no difference in attenuation between the groups at 24 weeks. Substantial improvements in variables associated with an anabolic response such as strength and physical function were also observed.

Castaneda et al. examined the effects of a low-protein diet with or without PRT in a 12-week RCT of patients with chronic renal insufficiency. Despite the protein restriction, trained subjects had significantly greater improvement in several measures of muscle strength (average, 32% increase) compared to a 13% decrease in nonexercising subjects. In addition, the trained subjects exhibited maintenance of body weight and increased total body potassium and type I and II muscle fiber areas, whereas controls were observed to undergo a decrease in these measures; the differences in the changes were statistically significant [79].

In a 24-week study, Chen et al. demonstrated that MHD patients randomized to low intensity (sic) PRT (about 60% of their maximal voluntary strength) for the lower extremity conducted during the second hour of dialysis had significantly greater improvements in physical function (short physical performance battery, SPPB), knee extensor strength, and physical activity levels than subjects in the attention control group [80]. Similarly, some but not all studies of patients with CKD randomized to PRT, with or without added ET, showed significant improvements in muscle strength, 6-minute walk distance, stair climb performance, sit-to-stand transitions, self-reported physical function, and quality of life. Even an interdialytic modified yoga program resulted in significant improvements in handgrip strength relative to controls [81].

A recent systematic review and metaanalyses of seven RCTs assessed the effect of PRT on muscle strength (seven studies, $N = 249$), skeletal muscle hypertrophy (six studies, $N = 200$), and health-related quality of life (HRQoL) (six studies, $N = 223$) patients with CKD stages 3–5 [9]. Studies were conducted over 8–24 weeks (average 14 weeks) with 3 days/week of training for six of the seven studies. Standardized mean differences (SMD) were used as an estimate of PRT effect relative to controls. Patients participating in PRT significantly improved standardized muscle strength (SMD = 1.15) and HRQoL (SMD = 0.83); the SMD for total muscle mass was 0.29 but was not significant. This is consistent with other studies of the PRT effect on LBM in CKD patients.

Limited and often inconsistent data do suggest significant anabolic effects in the form of increased muscle CSA, muscle fiber size, muscle growth factors, and their transcriptional levels, as well as decreased levels of myostatin and atrophic fibers from PRT interventions, particularly when combined with aerobic exercise training. Importantly, these changes are generally observed with improvements in less proximal measures of anabolism (i.e., muscle function and physical performance) that are of important functional benefit.

Observational data suggest that regular physical activity may be beneficial for improving survival in MHD patients who typically are extraordinarily inactive [4,82]. One report showed 35% less activity than in sedentary healthy individuals [83] and two studies that analyzed physical activity data reported by over 2200 HD patients in the United States Renal Data System Dialysis Morbidity and Mortality Study Wave 2 reported a 62% greater mortality risk in patients who were sedentary (never or almost never exercised) versus nonsedentary (i.e., those with physical activity on <1 day/week to daily) at the time dialysis was initiated [38,84]. Although a causal relation is not yet proven or tested, the associative data so far available suggest that increasing $\dot{V}O_2$ peak, muscle performance, physical function, and habitual physical activity in patients with CKD should be a high priority in their usual care, and specific exercise training and physical activity guidance should be considered part of routine therapy for the advanced CKD patient. Conspicuously lacking, however, are data on the sustainability of these positive changes, and whether there is sustained improvement in important health outcomes, such as survival, morbidity, and risk factors, especially cardiovascular risk factors [64]. Since most available data are based on studies of <6 month's duration, longer studies are needed to demonstrate whether sustainability of benefit does occur.

Results of studies examining the effect of exercise on urea clearance (Kt/Vurea) are mixed. Two studies found no change in Kt/Vurea after 8–16 weeks of moderate, 30- to 45-minute, cycle exercise during the HD procedure [85,86]. However, the effectiveness of exercise training on urea clearance may not have been optimized in these studies, since exercise was conducted into the third hour of dialysis. In one 8-week study, 10–30 minutes of either aerobic or resistance exercise during HD had no effect on Kt/Vurea [87]. It is possible that the 10- to 30-minute aerobic or RT used in this study was of insufficient time or intensity to observe an effect on Kt/Vurea. Conversely, three studies reported 5%–19% improvements in Kt/Vurea [51,88,89]. A 2019 systematic review of the effect of intradialytic exercise on HD adequacy concluded that there was no overall exercise effect on Kt/Vurea although 6 of the 13 trials demonstrated medium-to-large effect sizes. Exercise did have an overall beneficial effect on phosphate removal. Interpretation of findings is difficult due to inconsistencies in the designs of the included studies, for example, RCTs (three), crossover (eight), or single group (two), and widely different exercise training regimens [90].

The possibility of improved dialysis efficacy shown in some studies might engender benefits for skeletal muscle and provide another advantage for intradialytic, as opposed to interdialytic exercise training [7]. However further research is needed wherein the exercise stimulus is optimized in RCTs.

Principles of exercise training

There is an urgent need to establish expertly delivered, systematic, and regular exercise training in the CKD population. Members of the renal care team involved in recommending or delivering these programs should be aware of the basic principles of exercise that underpin effective exercise program design and progression. The principles of *Specificity*, *Overload*, *Progression*, *Individualization*, and *Reversibility* are summarized in Table 51.2.

TABLE 51.2 Summary of general principles of exercise training.

Specificity	The human body adapts or changes specifically to the type of training (physical stressor) imposed. For example, progressive resistance exercise training, PRT, is the preferred training modality to address loss of muscle mass and the ensuing muscle weakness [77,78] typical of individuals with advanced CKD. Unless one is very debilitated, aerobic exercise training is far less effective
Overload	"Overload" used in the context of exercise training defines a positive and necessary principle of "dose": without increasing effort beyond the usual, little to no improvement will occur
Progression	For adaptations to improve, there must be overload as described previously. Progression is repeated overload until targets for risk reduction, physical function, or other clinically or patient-important outcomes are achieved
Individualization	Each person has unique physical capabilities and limitations due to age, medical history, exercise history, comorbidities, years on dialysis, etc. The exercise dose must be individually developed, applied, and monitored for responsiveness. They should be dynamic with the dose altered as the individual responds to the training stimulus
Reversibility	Failure to maintain a regular training schedule will result in loss of improvements. This occurs quickly in older adults and in people with chronic disease. Patients should be encouraged to remain as regular as possible with their exercise routines even if not with the recommended duration and intensity

CKD, Chronic kidney disease; *PRT*, progressive resistance training.

The Frequency, Intensity, Time, and Type principle

Exercise training guidelines include specific variables for determining the exercise training dose. These are often referred to as the FITT principle: Frequency, Intensity, Time (duration of session), and Type of training. These variables may be manipulated for use in healthy individuals as well as in people with most chronic diseases, based on their ability. This is true for any type of exercise, including aerobic and resistance exercise training and flexibility, postural stability, and balance.

Warm-up

The warm-up is designed to stimulate blood flow to the active muscles, increase body temperature, and enhance free, coordinated movement. Depending on the planned exercise intensity, a general 5- to 15-minute whole-body warm-up of gradually increasing intensity to the intensity target should precede the conditioning period. At rest, muscle receives only about 15%–20% of the cardiac output; during moderate exercise, this increases to about 70%. Beneficial effects of warm-up include increased muscle temperature through increased blood flow, increased myocardial blood flow, rightward shift of the oxyhemoglobin dissociation curve facilitating oxygen delivery, and possible reduction in cardiac dysrhythmias [80]. For resistance exercise, movement through the intended range of motion for the selected exercise with light resistance will provide a muscle-specific increase in blood flow and temperature and improved neuromuscular activation, greater conduction velocities, and faster activation of muscle fibers [81].

Cooldown

In upright exercise a gradual decrease in exercise intensity over a 5- to 10-minute period prevents blood pooling in the lower extremities by maintaining the action of the peripheral muscle pump. Possible consequences of blood pooling include hypotension, fainting, and cardiac dysrhythmias [77]. Cooldown also facilitates heat dissipation and more rapid removal of lactic acid and catecholamines from the blood. Especially for dialyzed patients, a prolonged cooldown should be implemented to reduce the risk of hypotension following exercise and an emergency plan for episodic hypotension should be established and familiar to all of the health-care team working in the dialysis unit [90].

Patient assessment

Assessing patients with CKD provides objective insights into their physical abilities, helps to quantify exercise tolerance, aids in developing exercise training guidelines, and provides a baseline for monitoring progress and program efficacy [47]. These assessments may also be used to identify relationships between exercise intensity and symptoms such as cardiac abnormalities or musculoskeletal limitations.

Common assessments associated with exercise training and physical performance include measures of aerobic function (cardiorespiratory endurance), muscle performance, flexibility, and, in older individuals and in patients with chronic diseases, measures of physical function [4,91–94]. Table 51.3 summarizes several options for assessing health-related fitness and physical performance.

Aerobic function and cardiopulmonary endurance

Assessment instruments for endurance performance include laboratory methods such as CPXT using incremental and constant work rate (CWR) protocols performed on treadmills or cycle ergometers [47,95]. Analysis of gas exchange data collected with metabolic measurement systems adds precision and allows evaluation of the integrated function of the cardiovascular, pulmonary, and muscular systems [47,48]. Key variables to measure during this assessment include peak oxygen uptake ($\dot{V}O_2$ peak), the oxygen uptake ($\dot{V}O_2$) at the anaerobic (lactate) threshold ($\dot{V}O_2\theta$), as well work rate and heart rate at the time these markers of aerobic performance are obtained. Subjects' perception of effort using the subjective Borg 6–20 Rating of Perceived Exertion (RPE) scale [96], the Borg 0–10 category-ratio scale [97], the OMNI (omnibus) scale (a pictorial scale with ratings from 0 to 10 for cycling [98]), walking/jogging [99], and resistance exercise [100] or arbitrary 0–10 scales [39,101] aid the clinician in understanding the patient's perception of effort relative to objective physiologic indices. Additionally, these subjective data can be used later in designing exercise intensity prescriptions. Specific guidelines for administering and interpreting cardiopulmonary exercise tests assessments (CPXT, CWR, functional tests) have been published [14,48,102].

Because of the frequent occurrence of severe muscle weakness, most advanced CKD patients terminate an exercise test because of leg fatigue before a plateau in oxygen uptake is achieved, thus not meeting the primary criteria defining maximal oxygen uptake [46]. In addition to limitations in oxygen delivery (low hemoglobin, decreased cardiac output), there is often overall smaller muscle mass. In addition, advanced CKD/MHD patients, in comparison to healthy controls, often have dysfunctional mitochondria with impaired oxygen extraction due to significantly reduced cytochrome *c* oxidase activity, the catalyst for the final step in

TABLE 51.3 Methods for assessing dimensions of health-related fitness and physical performance in patients with chronic kidney disease.

Methods of assessment	Outcome variable(s)	Equipment	Dimension of performance	References
Cardiopulmonary function and endurance				
CPXT or cardiac stress test	$\dot{V}O_2$ peak	Treadmill or cycle ergometer metabolic measurement system	Aerobic capacity	[47,48]
	WR peak		Work capacity	
	HR peak		Chronotropic response	
	Anaerobic threshold		Ability for prolonged work	
	CPXT duration		Surrogate for aerobic capacity	
CWR	CWR duration	Treadmill or cycle ergometer	Submaximal aerobic endurance	
Muscle performance				
3-RM/5-RM (RM is repetitions at maximum resistance)	Strength	Elastic, free weights, or machine weights	Surrogates for muscle strength	[76,122–124]
Handgrip		Handgrip dynamometer		[240–242]
Repetitions to failure at 80% x-RM[a]	Fatigability	Elastic, free weights, or machine weights	Local muscle endurance	[32]
Physical performance—objective measures				
SPPB	0–12 score	4-m walk course	Physical function	[138]
NSRI-PF[b]	Time		Integrated physical function	[243]
Chair stands	Time or number of stands	Chair; stopwatch	Physical function; surrogate for leg power	[145]
Stair climb	Time and power	Staircase; timing system	Physical function; surrogate for leg power	[129]
Lift and lower	Number of shelves	Shelves; weight	Upper extremity physical function	[146]
6-MWT	Distance and gait speed	20- to 30-m straight course	Physical function; gait speed	[106]
Timed walks	Gait speed	Measured course 6- to 400-m	Gait speed	[143]
TUG	Time	Chair, measured course	Integrated physical function	[244]
Flexibility				
Forward trunk flexion	Centimeters reached	Sit-and-reach box	Integrated flexibility	[132–134]
Rotational trunk flexion	Centimeters reached	Meter stick	Rotational flexibility	
Balance				
Single leg balance	Time in balance	Stopwatch	Balance	[138]
Semitandem balance	Time in balance	Stopwatch	Balance	[138]
Berg balance test	Berg score	Step stool, mat table, chair with arms	Balance	[245]
		Tape measure, stopwatch, and pen		
Timed tandem walk	Time and errors	6-m course; stopwatch	Dynamic balance	[246]

(*Continued*)

TABLE 51.3 (Continued)

Methods of assessment	Outcome variable(s)	Equipment	Dimension of performance	References
Physical activity objective measures				
Pedometers	Step counts	Pedometer	Spontaneous PA	[247]
Accelerometers	Step counts; time in different activity levels	Accelerometer (Triaxial)		[248]
Physical activity subjective measures				
KDQOL				[249,250]
SF-36				[251]
PF-10				

6-MWT, 6-minute walk test; *CPXT*, cardiopulmonary exercise test; *CWR*, constant work rate test; *HR*, heart rate; *KDQOL*, Kidney Disease Quality of Life; *PA*, physical activity; *SPPB*, short physical performance battery; *TUG*, timed-up-and-go; *WR*, work rate.

[a] *x-RM indicates the use of the number of repetitions used to assess strength. This could be one repetition (1-RM), three repetitions (3-RM), etc. For the fatigue test, 80% of 1-RM or 3-RM is this example would be used.*

[b] *NSRI-PF is North Staffordshire Royal Infirmary Physical Function Test. See Ref. [243].*

mitochondrial oxidative phosphorylation [103]. Hence, $\dot{V}O_2$ peak is considered the index of functional capacity in advanced CKD patients. Painter correctly points out, however, that $\dot{V}O_2$ peak may not reflect the functional impact of exercise training in MHD patients [104]. Maximal incremental exercise testing investigates the limits of exercise tolerance, not the functional capabilities of work more commonly encountered in everyday life [105]. Submaximal CWR tests are particularly appealing in this regard, since these tests assess one's ability to sustain exercise at submaximal levels. In one study investigating the effects of 9 weeks of cycling exercise in MHD patients, $\dot{V}O_2$ peak increased by 22% [32]. However, endurance time with a CWR test performed at 80% of baseline peak work rate increased by 144%, from 5.5 to 13.4 minutes. Improvements in $\dot{V}O_2$ peak predict increased capacity for exercise and reduced health risks, but the large increase in CWR time suggests the potential for substantial improvements in the ability to perform everyday activities that may lead to improvements in quality of life.

When CPXT with gas exchange analysis is not feasible or is inappropriate, incremental and CWR cycle or treadmill tests can still be performed while monitoring blood pressure (BP), heart rate, electrocardiogram, and work rate. Time to peak exercise provides an index of functional capacity and peak work rate reflects exercise tolerance. Symptoms of exercise intolerance, including BP and ECG abnormalities, at submaximal work rates may be useful in setting exercise training intensities to avoid these signs and symptoms of intolerance.

Functional exercise tests such as 6-minute walk distance test [106,107] and shuttle walk test [108,109] are practical, time-saving, inexpensive and can provide helpful information for setting the exercise prescription and for progress monitoring. Specific guidelines for administering the 6-minute walk test (6-MWT) and the shuttle walk test are available [106,109].

Muscle performance

Muscle performance includes three specific functional attributes: strength, power, and fatigability (local muscle endurance). Maximal voluntary *muscle strength* is the greatest force that can be developed against a resistance. Testing for strength in healthy individuals is often attempted only once at a time to assess maximum strength; this technique is referred to as the one-repetition maximum (1-RM) procedure [110]. This method requires a gradual progression of increasing resistance to muscular movement to the maximum resistance that can be overcome for one repetition only. The 1-RM procedure has been administered safely in older people [32,69,111], and in people with various chronic disease states, including patients with COPD [112,113], cardiac patients [114–116], and CKD patients [7,78,117]. However, 1-RM tests may not be routinely appropriate for use in the ESRD population due to the higher risk for fracture and tendon rupture [118,119]. Spontaneous tendon ruptures have been reported in MHD patients [119] and tend to be associated with hyperparathyroidism and not with exercise. Nevertheless, caution is needed when assessing or training maximal muscle strength or power and should only be done by trained and experienced personnel. Alternatives to the 1-RM test include the 3-RM [76] or 5-RM [77,120,121] procedure in which resistance is gradually increased to the maximum level at which three or five repetitions can be performed in good form, and above which the resistance can no longer be overcome. The 3-RM and 5-RM have been shown to predict 1-RM with reasonable accuracy in healthy individuals [122–124], but no studies have examined this prediction in CKD patients.

Muscle power defines the rate at which a muscle or muscle group performs work and can be expressed as force × velocity. Power is associated with a variety of physical performance measures, including sit-to-stand transitions, stair climb time, and gait speed [32,125,126] and may be a better predictor of functional performance than strength [127–129]. Despite its strong association with physical performance, this metric of muscle performance has not been reported in resistance exercise training studies with CKD patients. This may be due in part to the technical difficulty of measuring muscle power without specialized equipment and the risk of muscle/tendon injury. A safe alternative that may be used as a surrogate for leg power measurements is the time taken to complete a number of sit-to-stand transitions (e.g., 5–10) [130].

Muscle fatigability is a measure of muscle endurance and the ability to sustain effort over time. Targeted exercises using a standardized resistance of 70%–90% of the 1-RM, 3-RM, or 5-RM can evaluate the ability of a particular group of muscles to make repetitive contractions at submaximal loads before fatigue leads to failure to complete the next repetition. Musculoskeletal limitations can be further evaluated and possibly treated through referral to a physical therapist or exercise physiologist. Assessment of muscle strength, muscle endurance, or muscle power may be used to develop the RT prescription, for monitoring progress, or to evaluate program efficacy. When used for these purposes, the type of resistance (Table 51.3) and movement pattern use for the assessment exercises should be identical to those used in training.

Flexibility

Loss of flexibility contributes to restricted mobility in daily activities, particularly in older individuals. Since no single measurement indicates loss of flexibility at all joints [131], multiple or integrated tests of flexibility can be considered. The modified sit-and-reach test [132] primarily assesses hamstring flexibility and to a lesser extent, low back and calf flexibility in the sagittal plane; the standing trunk rotation test assesses the integrated flexibility of the ankles, knees, trunk, shoulder, and neck in the horizontal plane [133,134]. Test–retest reliability for these tests is high, $r = 0.83$; interclass reliability is 0.98–0.99 in older adults [131,134,135].

Physical function

Aging and chronic disease often bring about diminished physical function that contributes to increased risk of falls, fractures, disability, hospitalization, poor quality of life, and mortality [136–141]. Indeed, physical function has been described as a mirror to an individual's health. [127,142–145]. Objective measures of physical function reflect the ease with which one performs typical activities of daily living, including walking, stair climbing, rising from a chair, and lifting and lowering objects. Many of these tests have been developed for frail older people [126] and as such often have ceiling effects when applied to other populations [146–148]. That is, when a person's ability reaches a certain level, they may have attained a maximum score with some tests; therefore no further improvement in the test scores is seen with increased ability. However, given the low functional ability of people with advanced CKD compared with healthy controls [149], many of the common tests of physical function may be entirely appropriate for this population. Several of these measures are summarized in Table 51.3.

Overend and colleagues studied the relative and absolute reliability of the 6-MWT and the number of sit-to-stand transitions completed in 30 seconds in a convenience sample of 25 men and women with ESRD [150]. Interclass correlations for the two functional measures were good (0.93 for both), suggesting good reliability, but the significant differences between trial 1 and trial 2 for the 6-minute walk (19-m) and chair stands (one repetition) suggest that it is important to use duplicate trials for these tests to ensure baseline stability. The minimal detectable changes determined from these data were 77 m for the 6-MWT and 2.6 repetitions for the chair stands.

The relative and absolute reliability of three physical function tests, the SPPB, the timed-up-and-go (TUG), and the one-legged stand test (OLST), were recently determined in 71 individuals receiving HD [91]. Participants were 21–90 years of age and performed duplicate trials for each test 2 weeks apart. Interclass correlations were ≥0.90. Minimal detectable change scores at 90% confidence intervals for these tests were 1.7 points for the SPPB, 11.3 seconds for the OLST, and 2.9 seconds for TUG. It is important to note that the above noted minimal detectable changes are specific to the MHD population. Since the minimal detectable difference describes the random variability in scores of a truly stable participant, changes greater than these values can give confidence that a true change will have occurred within a stated confidence interval. Since the minimal detectable difference describes the random variability in scores of a truly stable participant, changes greater than these values can give confidence that a true change will have occurred 95% of the time.

Self-reported physical function has also been evaluated in MHD patients. Knight et al. reported hazard ratios for 1-year mortality in 15,000 MHD patients using the physical component summary (PCS) from the SF-36 [151]. Compared to patients with a PCS score >50, individuals scoring 20–29 had a mortality hazard ratio of 1.62; those scoring 30–39 had a hazard ratio of 1.32, and patients whose PCS was <20 had a hazard ratio of 1.97. Patients whose PCS declined over 1 year had additional risk of mortality with an increased hazard ratio of 1.25 per 10-point decline in PCS score.

MacKinnon et al. systematically reviewed 29 studies in nondialyzed CKD patients exploring the association between survival rates and physical function (12 studies) or physical activity (17 studies) [4]. Self-report inventories reported in the review included the HRQoL [152] and Kidney Disease Quality of Life measure [153]. Overall, the authors reported a clear pattern of higher mortality rates or adverse clinical events with lower physical function and physical activity levels regardless of the instrument used for their assessment.

Objective measures of physical function are most desirable, but pragmatically, they require clinic time personnel and equipment. Alternatively, self-reports can be quickly administered in a clinic waiting room and provide a practical method of assessing the patient's functional status that correlates with morbidity and mortality [4].

Application of exercise training program design for patients with CKD

The optimal dose of exercise training for advanced CKD patients is unclear [17,18,154]. Research shows large variability in responsiveness largely due to program design, execution, and individual differences [18]. However, analyses of recent studies and published recommendations from authorities on exercise for the CKD population [7,50,155,156] have helped disentangle inconsistencies in exercise training recommendations for people with CKD. This has evolved into an evidence-based position statement on exercise in CKD [17] and an expert statement on exercise for people with CKD [18]. Guidelines for developing endurance (aerobic) exercise and progressive resistance exercise regimens for those with advanced CKD. These expert guidelines utilize the FITT principle and, like those for cardiac [70,95] and pulmonary rehabilitation programs [15,16], are patterned after existing, well-established guidelines for healthy younger [39] and older individuals [101] that have advanced since 1975 [157]. The 2008 [158] and 2018 [40] Physical Activity Guidelines for Americans from the US Department of Health and Human Services have contributed to the ease of understanding the guidelines and more widespread dissemination of the recommendations.

Objectives of exercise training for advanced CKD patients

Well-planned and systematic application of exercise training principles, setting clearly defined goals, and regular evaluation of physical functional ability are vital steps in establishing habitual exercise and increased physical activity. Strong encouragement from practitioners regarding these important behavior changes will help optimize improvement in fitness and physical function, risk reduction, and quality of life. Table 51.4 summarizes key steps for achieving these objectives.

When to exercise

Both intradialytic [31,32,51,52,76–78,80,85,104,159–165] and interdialytic [23,161,166–173] exercise training programs have been used successfully and safely in studies

TABLE 51.4 Objectives of exercise training for advanced chronic kidney disease (CKD) patients.

Assess individual patients for exercise history and physical functional abilities (see Table 51.3)
Develop safe and effective exercise training regimens and assist the patient in their successful implementation
Assist the patient in finding community resources for supervised exercise training. This could be a cardiac rehabilitation program
Provide guidelines for unsupervised exercise, for example, home exercise, as well as for lifestyle physical activity
Continually reinforce the importance of regular physical activity
Provide appropriate supervision and monitoring to detect changes in clinical status and provide ongoing surveillance data to the patients' health-care providers to enhance medical management
Progressively increase exercise capacity, physical function, quality of life, and survival
Decrease risk factors associated with CKD and ESRD
Provide patient and family education to maximize secondary/tertiary prevention, for example, risk factor modification

ESRD, End-stage renal disease.

of MHD patients. In general, supervised programs are preferable, when possible. If training is conducted during an HD session, it should be done either before or during the first 90–120 min of treatment to avoid the risk of hypotensive responses. Unsupervised home programs have had mixed success.

Three studies have directly compared home versus supervised intra- or interdialytic exercise on various primary outcomes, including $\dot{V}O_2$ peak, $\dot{V}O_2$ at the anaerobic (lactate) threshold, 6-MWT distance, and aortic pulse wave velocity [161,162,174]. Patients randomized to supervised programs on nondialysis days had the greatest improvement from baseline in aerobic capacity, but they incurred the highest dropout rates as compared with intradialytic training. Some improvement in the primary outcomes was demonstrated in all three of the exercise training schedules.

Parsons and King-VanVlack suggested that in addition to the attributes noted previously, exercise during dialysis may increase dialysis efficacy [64]. Movements of solutes from tissues to blood that then circulate through the hemodialyzer are rate-limiting steps for the removal of many solutes, including uremic toxins. Exercise increases cardiac output and capillary blood flow, and thus exercise during HD may enhance the removal of dialyzable metabolites from tissues [29]. Thus intradialytic exercise may be the preferred exercise time, since it not only provides increased opportunity for supervision and adherence and makes use of what is otherwise a long bout of sedentary time, but it may increase dialysis efficiency. Moreover, by the end of the dialysis procedure, the individual is often fatigued and less willing to exercise later in the day.

Guidelines: endurance exercise training for CKD patients

Current endurance exercise training guidelines for people with advanced CKD are summarized in Tables 51.5 and 51.6. For comparison, evidence-based guidelines for healthy younger and older individuals as well as for patients with CVD and COPD are included.

TABLE 51.5 Summary of evidence-based guidelines for endurance exercise prescription in chronic kidney disease (CKD). Included for comparison are evidence-based guidelines for individuals with cardiovascular disease and healthy younger and older adults.

Group	Frequency (day/week)	Intensity	Time (min)	Type	Notes
Exercise & Sports Science Australia (ESSA) [17]		*Interdialysis*			
	≥3	55%–70% HRmax; RPE = 11–13 (6/20 scale) Prefer >60% HRmax	Build up to 30–45	Walking, cycling, other large muscle group exercise	Nondialysis days Build up to 180 min/week
		Intradialysis			
	3	55%–90% HRmax; RPE = 11–16 (6/20 scale) Prefer >60% HRmax	Build up to 30–45	Cycling	Exercise during the first 2 h of dialysis
		Nondialyzed			
	≥3	55%–70% HRmax; RPE = 11–13 (6/20 scale) Prefer 60%–90% HRmax	Build up to 30–45	Walking, jogging, cycling, other prolonged, rhythmic, large muscle group exercise	Adjust exercise dose according to patient needs
British Association of Sport and Exercise Sciences (BASES) [18]	≥3 Advise regular daily physical activity	"Moderate" *ACSM criteria*: 40–<60% $\dot{V}O_2$ reserve (see Table 51.4) RPE = 11–13/20	Individually determined	Cycling	Time examples: 15 min in intervals, for example, 3 × 5 min 20 min in intervals, for example, 2 × 10 min 20–30 continuous min

(*Continued*)

TABLE 51.5 (Continued)

Group	Frequency (day/week)	Intensity	Time (min)	Type	Notes
American College of Sports Medicine (ACSM) [95,252]	3–5	Moderate: 40%–59% $\dot{V}O_2$ R; RPE 12–13 on Borg 6–20 scale	20–60 continuous activity; if unable to perform exercise continuously, 3–5 min intervals with goal to accumulate 20–60 min	Prolonged, rhythmic activities using large muscle groups (walking, cycling, swimming)	Depending on clinical status and functional capacity, initial intensity should be light, for example, 30%–39% $\dot{V}O_2$ R; If intervals are used start with 1:1 work:rest ratio; initial training time can be set to 15 min and increased as tolerated to achieve 20–60 min
Special considerations during hemodialysis			Ideally, exercise nondialysis days; HR may be unreliable—use RPE to monitor intensity; Exercise during the first half of dialysis to avoid hypotensive episodes; avoid exercising arm with permanent A-V access		
Metaanalysis exercise in CKD [8]	3	"High intensity"	30–90 (includes RT)	Large muscle group, sustained exercise, for example, leg cycling, walking, jogging	These summary recommendations were stated as the strategy to "increase aerobic capacity as effectively as possible" and includes the recommendation of a 4- to 6-month supervised program
Cardiac rehabilitation (outpatient) [14,95]	Minimum = 3 Prefer ≥ 5	If CPXT data are available: 40%–80% HRR or $\dot{V}O_2$ R or $\dot{V}O_2$ peak; Without CPXT[a]: HR rest + 20–30 bpm OR RPE = 12–16 (Borg 6–20 scale) RPE = 11–14; 40%–80% HRreserve or $\dot{V}O_2$ reserve Target heart rate < angina, ST-depression, BP thresholds; to tolerance	20–60	Large muscle group, sustained exercise, for example, walking, leg cycling, arm cycling, arm and leg cycling, rowing	Intermittent, short-duration exercise may be necessary initially; both continuous and interval training may be used
Healthy younger [32]	≥ 5 ≥ 3 3 + 2 ≥ 3	Moderate[b] or Vigorous or Moderate + vigorous	30–60 20–60	Large muscle group, sustained exercise, for example, walking, jogging, leg cycling, arm cycling, arm and leg cycling, rowing, swimming	Target volume recommendations: ≥ 150 min/week, higher amounts bring better results
Healthy older [72]	≥ 5 ≥ 3	Moderate (5–6/10)[c] and Vigorous (7–8/10)[c]	≥ 30 ≥ 20	Large muscle group, sustained exercise, for example, walking, jogging, leg cycling, arm cycling, arm and leg cycling, rowing, swimming	Duration should be accumulated in bouts of ≥ 10 min Duration should be continuous for ≥ 20 min/day

BP, Blood pressure; *CPXT*, cardiopulmonary exercise test; *HR*, heart rate; *HRR*, heart rate reserve defined as (HRmax−HRrest); *RPE*, rating of perceived exertion; *Target Heart Rate*, heart rate recommended during exercise training; $\dot{V}O_2R$, oxygen uptake ($\dot{V}O_2$) reserve defined as ($\dot{V}O_2$max − $\dot{V}O_2$rest).

[a] CARDIAC: *If maximal exercise test data are not available, THR = HRrest + 20 bpm with increases based on RPE, signs and symptoms, and normal physiologic responses.*

[b] Healthy younger adults (18–65 years): *Moderate intensity is 40%–59% HRR or $\dot{V}O_2R$; 64%–76% HRmax; 46%–63% $\dot{V}O_2$max; RPE = 12–13/20 (fairly light to somewhat hard). Vigorous intensity is 60%–89% HRR or $\dot{V}O_2R$; 77%–95% HRmax; 64%–90% $\dot{V}O_2$max; RPE = 14–17/20 (to somewhat hard – very hard). More favorable results are seen at higher intensities.*

[c] Healthy older adults (≥65 years): *Moderate intensity is 5–6 on a 10-point scale. Vigorous intensity is 7–9 on a 10-point scale. Moderate and vigorous training may also be mixed when appropriate. More favorable results are seen at higher intensities.*

TABLE 51.6 Methods for calculating relative endurance exercise training intensities and their equivalencies.

	% HRmax	% $\dot{V}O_2$ max	% HRreserve or % $\dot{V}O_2$ reserve	RPE 6–20 [96]	RPE 0–10 [97]
Very light	<57	<37	<30	<9	0–1
Light	37–45	37–45	30–39	9–11	2–3
Moderate	64–76	46–63	40–59	12–13	3–4
Vigorous	77–95	64–90	60–89	14–17	5–7
Near maximal to maximal	≥96	≥91	≥90	≥18	8–10

%HR rate reserve is HRmax − HRrest; % $\dot{V}O_2$ reserve is $\dot{V}O_2$ max- $\dot{V}O_2$ rest; RPE 6–20 is Borg's rating of perceived exertion (RPE) Scale [96]; RPE 0–10 is Borg's Category-Ratio Scale of perceived effort and pain [97].

Adapted from Garber CE, Blissmer B, Deschenes MR, Franklin BA, Lamonte MJ, Lee I-M, et al. American College of Sports Medicine position stand. Quantity and quality of exercise for developing and maintaining cardiorespiratory, musculoskeletal, and neuromotor fitness in apparently healthy adults: guidance for prescribing exercise. Med Sci Sports Exerc 2011;43:1334–59. https://doi.org/10.1249/MSS.0b013e318213fefb.

Frequency

Frequency defines the number of days/week for exercise and may vary with the medical and exercise history of the individual as well as with acute exacerbations. Training frequency may be different for different types of exercise, for example, aerobic and RT, although two or more types of exercise might be performed in a given session. For example, flexibility, endurance exercise, and resistance exercise could be performed during the same visit to the dialysis center.

Overall, patients with CKD should target endurance exercise of moderate duration on 5 or more days/week. Initially, 3 days/week might be an appropriate target to gradually adapt to unaccustomed exercise and to contribute to compliance. As fitness improves, achieving the evidence-based guideline of 5 days/week is recommended. For MHD patients, intradialytic exercise may be preferred where there is the availability of supervision in facilities that offer exercise training; this may improve compliance. When feasible, additional interdialytic exercise and physical activity should be recommended, ideally with supervision and guidance, but home exercise, such as walking or stationary cycling and/or modest resistance exercise training, should also be recommended. Logs of training sessions will assist practitioners in monitoring compliance and provide rationale for adjusting components of the patient's exercise training program.

Intensity

Intensity refers to the level of exertion during exercise. Intensity can be prescribed and measured objectively or subjectively and may be expressed differently for different types of exercise. Examples of intensity metrics for different types of exercise are described next and summarized in Table 51.6.

Endurance exercise training for MHD patients should begin with lower intensities and progress to higher intensity as tolerated and safe. Evidence in healthy individuals suggests that intensity as low as 30% $\dot{V}O_2$ peak or RPE of 10–11 would be an appropriate starting point for these patients [175–177]. Although some research studies have used percentage of HRmax to guide training intensity in MHD subjects [86,104,162,163,169], it may be difficult to do so in these patients because of conditions such as underlying heart disease, especially with arrhthymias, autonomic dysregulation, changes in blood volume [178], medications such as ß-blockers and some calcium channel blockers [95], and noncardiac-related limitations to exercise such as pulmonary disease [47] or myopathy [23,179,180]. The use of prediction equations from submaximal exercise variables, such as peak exercise time or treadmill speed and grade [181], or one of the commonly used HRmax prediction equations such as 208−0.7 × age (years) [182] to predict HRmax may be employed to select initial levels of exercise intensity [183,184]. A caveat to prediction of HRmax is the attendant prediction error that may be >10 bpm [184]. Performing a clinical exercise test to peak exercise would improve the usefulness of heart rate indices for intensity prescription, since an actual HRpeak would be obtained by this method. When the test is repeated with similar peak efforts, the reproducibility of HRpeak is about ±2 bpm. While this approach might be most useful in nondialyzed CKD patients, even objectively determined HR indices for training intensity for MHD patients may not be as reliable as other objective measures such as $\dot{V}O_2$ or work rate (WR), if these data are available and are feasible to use. If objective data are not available to set the training intensity, use of one of the perceptual scales such as the Borg scales [96,97], the OMNI scales [98,99], or the 0- to 10-point scale advocated for healthy older individuals [101] could be used. Table 45.6 summarizes several approaches to objectively and subjectively determine exercise intensity. Light-to-moderate levels of exertion would be the most appropriate choices for most MHD patients, at least until exercise becomes regular and fitness improves. At this point, higher intensity work might be introduced.

An example of a novel low-intensity exercise program administered at home was recently reported by an Italian group studying the efficacy of a 24-week low-intensity home walking program versus usual activity in 296 MHD patients [185]. Participants randomized to walking did so on 3 nondialysis days for 10 minutes twice each day in bouts of 5 minutes walking then 1-minute rest, repeated twice; the least fit group did five bouts with a 2:1 walk:rest ratio. Intensity was based on stepping cadence that was individualized using baseline 6-MWT distance. Cadence was set by a clip-on metronome given to each participant. Compared to controls, the walking group had significantly greater improvements in 6-minute walk distance, time to complete five sit-to-stand transitions, and scores on a kidney disease-specific QoL inventory. Dropouts from the walking group were more than twice as great as in the control group, 31% versus 14%. The entire program was managed by the dialysis staff who had been trained by the research team. Using step cadence as a measure of intensity was a clever, simple way to guide intensity.

High-intensity interval training (HIIT) is another option for more fit individuals with CKD. HIIT uses alternating bouts of higher and lower intensity exercise that has been used safely and effectively as a time efficient alternative to improve aerobic capacity in healthy people [186], in patients with COPD [187–189], heart disease [190–192], cardiometabolic diseases [193,194] and advanced CKD [195,196]. Examples of HIIT include high-intensity intervals of 80%–105% $\dot{V}O_2$ peak alternated with lower intensity intervals (70%–70% $\dot{V}O_2$ peak) in various ratios, for example, 1:1, 1:2, 4:3, 0.5:4 repeated four to six times. Burgomaster et al. trained eight healthy young men and women using four to seven 30-second maximal efforts on a cycle ergometer interspersed with 4-minute recovery periods [186]. A total of six training sessions were evenly distributed over 2 weeks. A control group did not train. Time to fatigue at work rates equivalent to 80% baseline $\dot{V}O_2$ peak increased by 100% with no change in controls. This impressive improvement in endurance occurred after an average total high-intensity exercise time of 14–16 minutes and a total training time, including the rest intervals, of about 90 minutes over 2 weeks suggesting the time efficiency of this training method. Hwang et al. summarized findings of six RCT using HIIT compared with moderate-intensity continuous training (MICT) in cohorts of patients with cardiometabolic diseases [193]. Total energy expenditure between HIIT and MICT groups was held equal. Adherence to HIIT was between 70 and ≥90%. Compared to continuous MICT, HIIT yielded significantly greater improvements in $\dot{V}O_2$ peak; the weighted mean difference was 3.6 [95% confidence interval (CI), 2.28–4.91] mL/kg/min.

To date, only two randomized trials have tested HIIT in CKD patients [195,196]. In one study, 20 MHD patients were randomized to 22 weeks of twice-weekly supervised HIIT, MICT, or usual care [196]. Exercise was performed on a cycle ergometer at the dialysis chair and included an 18-minute warm-up. The HIIT group then completed three intervals of 3 minutes each at 85%–95% of HRpeak (15–17 on the Borg scale) interspersed with 4 minutes of active recovery at 60%–70% HRpeak. A 10-minute cool-down followed the last high-intensity interval. After warm-up, subjects in MICT completed an additional 27 minutes of continuous cycling at 50%–60% HRpeak that represented 11–13 on the Borg scale. Three, five, and three subjects in HIIT, MICT, and usual care groups completed the study. Dropouts included five individuals who received a kidney transplant. This pilot study reported no adverse events, but due to baseline heterogeneity in $\dot{V}O_2$ peak, and the small sample size, it could not be concluded that the HIIT was superior to the MICT for improvement in $\dot{V}O_2$ peak, 6-minute walk distance, or HRQoL. Interestingly, two of the three people completing HIIT improved $\dot{V}O_2$ peak by 46% and 53% (group average +28%). Two of the five people in the MICT group improved by 18% and 36% (group average +4%). The median adherence for both exercise groups was 73%, and there was no difference between groups in enjoyment.

Another pilot study investigated the feasibility, safety, and efficacy of HIIT in stages 3 and 4 CKD patients by randomizing 14 such patients to 12 weeks of thrice-weekly treadmill exercise at HIIT or MICT [195]. The HIIT regimen consisted of four intervals of 4 minutes at 80%–95% HRpeak interspersed with 3-minute recovery intervals at 65% HRpeak. The MICT protocol required 40 continuous minutes of walking at 65% HRpeak. The study demonstrated that HIIT training was feasible and safe, but both groups exhibited similar changes in fitness measures, mitochondrial biogenesis or body composition. Subjects in both groups had similar adherence and reported the exercise as enjoyable. The authors stressed that safety was enhanced by thorough cardiac screening and a CPXT for all subjects prior to the study. Such screening may not be available in routine clinical practice suggesting great care when prescribing HIIT to CKD patients.

Although high-intensity exercise has been shown to be effective and safe in some patient groups, whether it is either appropriate, feasible, or effective for advanced CKD patients remains to be convincingly demonstrated. Since the prevalence of CVD in patients with advanced CKD is very high, it is strongly suggested that *every advanced CKD* *patient* undergo coronary artery stress testing before they start any exercise program that substantially increases oxygen consumption. Ideally, the stress test would include imaging or ultrasonic evaluation of cardiac perfusion or function during exercise conditions. This evaluation will help reveal whether an individual can safely undergo exercise training as well as the training dose. As patients accommodate to regular exercise training, the careful introduction of interval training can provide variety and a greater stimulus for improvement. Much more systematic study with interval training in advanced CKD patients is needed before it can be universally recommended.

Time (session duration)

Current evidence-based guidelines for endurance exercise time in healthy individuals [39,40,101] and non-CKD patient groups [13,16,95] suggest ≥30 minutes per session with a target of accumulating ≥150 minutes/week of endurance exercise training. An evidence-based position statement on exercise in CKD and an expert statement on exercise for people with CKD recommend building up to 30–45 minutes per session [17,18]. An individual's starting level of fitness and clinical status will help the clinician determine the appropriate starting session duration. An adage from the geriatric literature, "start low, go slow," is applicable here.

Thirty minutes of endurance exercise 5 days/week is a target milestone. Some CKD patients might be able to achieve this target from day 1. Individuals with more advanced CKD will likely need a shorter exercise time due to their significant deconditioning and low tolerance for exercise at least when starting ET. Examples include intervals in bouts of 5–10 minutes with total exercise time of 10–15 minutes. This can be progressed to longer bouts then continuously, as tolerated, to the target 30–40 minutes. Readers are referred to Ref. [18] for examples of initial short exercise session times that progress over 3 months for CKD patients.

Type

Cycle ergometry performed at the dialysis chair is the most practical type of endurance exercise during an HD session. Most commercially available cycle ergometers require slight modification or adjustments in positioning to provide effective yet reasonably comfortable training. Ideally, patients undergoing exercise training during the HD session should be in a semirecumbent position while exercising so as to reduce the risk of hypotension or falling. For interdialytic exercise, available and patient-preferred types of aerobic exercise may be used. Whereas walking might be the most readily available and easiest type of exercise, other exercise modes such as cycling, swimming, rowing, or arm cycling can be used. A metaanalysis of exercise training in MHD patients concluded that any mode of exercise training yielded a statistically significant difference in improvement in many health-related fitness and physical function measures when compared to nonexercising controls [7].

Rest interval

During the initial phases of the ET program, patients may need periodic rest so that they can accommodate the exercise even though it may be at low intensity. No fixed time can be recommended; however, the practitioner should encourage the patient to resume the exercise as tolerated while maintaining the recommended training intensity. Also, recovery days in the early training phases should involve either no or only light exercise. With adaptation, more consecutive days of moderate-intensity activity can be added to the target.

Progression

For CKD patients, increases in the duration of continuous exercise to target should be considered first. Afterward, increased frequency to target (ideally ≥5 days/week) is recommended followed by gradual increases in intensity. Dosing for exercise prescription is part science and part art. The well-trained practitioner should carefully monitor patient adaptations and provide guidance on when and how much to change exercise volume, the product of frequency × duration × intensity, which leads to calculation of MET-minutes or MET-hours per week. For example, 3 days of endurance exercise for 30 minutes/day (perhaps done continuously or in smaller bouts of time) × moderate-intensity exercise of three METs (leg cycling at about 20 W) [197] equal 270 MET-minutes/week. The target is ≥600 MET-minutes/week, for example, 5 days/week × 30 min/day × 4 METs. MET values for conditioning exercises can be found in the 2011 Compendium of Physical Activity, available in eight languages. It may be accessed at https://sites.google.com/site/compendiumofphysicalactivities/home or in a simplified version in English at https://download.lww.com/wolterskluwer_vitalstream_com/PermaLink/MSS/A/MSS_43_8_2011_06_13_AINSWORTH_202093_SDC1.pdf.

Guidelines: progressive resistance exercise training in people with CKD

Resistance training guidelines for advanced CKD and chronic dialysis patients are listed in Table 51.7. For comparison, evidence-based guidelines for healthy younger and older individuals as well as for patients with CVD and COPD are included.

TABLE 51.7 Summary of evidence-based and clinical practice guidelines for progressive resistance exercise training in advanced chronic kidney disease and maintenance hemodialysis patients, healthy young and older individuals, and cardiac patients.

Group	Frequency (days/week)	Intensity	Time (sets—reps)	Type	Exercises (number)	Notes
Exercise & Sports Science Australia (ESSA) [17]	*Interdialysis*					
	2 nonconsecutive days	12–15 RM or 60%–70% RM	1 set 12–15 reps	Weight-bearing activity; elastic bands or tubing; weight cuffs; dumbbells; weight machines	8–12 major muscle groups (MMG)	MMG: Quadriceps, Hamstrings, Calf Abdominals, Low back Pectorals, Latissimus dorsi Deltoids, biceps, triceps, Hip abductors and adductors
	Intradialysis					
	Before or during dialysis	12–15 RM or 60%–70% RM	1 set 12–15 reps	Weight-bearing activity; elastic bands or tubing; weight cuffs; dumbbells as practical	Up to 12 MMG	
	Nondialyzed					
	2 nonconsecutive days	12–15 RM or 60%–70% RM	1 set 10–15 reps	Weight-bearing activity; elastic bands or tubing; weight machines; free weights		
British Association of Sport and Exercise Sciences (BASES) [18]	2 nonconsecutive days	60%–70% 5-RM	2/3 sets 8–10 reps	"Resistance weights"	Dynamic leg exercise	Clinical status determines applications of the exercise guidelines
American College of Sports Medicine (ACSM) [95,252]	2–3 nonconsecutive days	65%–75% 1-RM testing 1-RM not recommended Use ≥3 RM to estimate 1-RM	Minimum 1 set 10–15 reps	Machines, free weights, bands	8–10 MMG	For most patients, target increasing sets as a goal
ACSM Healthy younger (18–64 years) [39,95]	2–3 nonconsecutive days	60%–70% 1-RM (novice) 80% 1-RM (experienced)	1–4 sets 8–12	A variety of equipment and/or body weight can be used	MMG	<50% 1-M to improve muscular endurance Rest intervals of 2–3 min between sets
Healthy older (≥65 years) [95,101]	2–3 nonconsecutive days	40%–50% 1-RM (novice) 5–6 on 10 point scale	≥1 set 10–15 reps	A variety of equipment and/or body weight can be used	8–10 MMG	Nelson et al. [72] recommend moderate (5–6) intensity exercise with vigorous intensity (7–8/10) as an option for more fit and experienced people, preferably with supervision
Cardiac rehabilitation (outpatient) [115]		30%–40% 1-RM (upper body) 50%–60% 1-RM (lower body)	1–3 sets 10–15 without significant fatigue	A variety of equipment and/or body weight can be used	8–10 MMG	See Williams et al. [98] for details and contraindications; training loads might increase to 50%–80% 1-RM

Frequency

Most existing guidelines suggest conducting PRT on 2 nonconsecutive days per week with the assumption that all major muscle groups are exercised on each of the 2 days. Major muscle groups include quadriceps, hamstrings, triceps surae (gastrocnemius and soleus), abdominals, erector spinae (and other low back muscles), latissimus dorsi, pectoralis major, deltoids, biceps, and triceps. If improvement in gait is a goal, exercise for the hip abductors and adductors and the gluteals should be added. When applied to patients exercising before or while undergoing MHD 3 days/week, it might be possible to enhance recovery with a more equal distribution of days, such as Monday and Friday or Tuesday and Saturday. People with CKD not receiving dialysis could improve the distribution of training days by performing PRT on Mondays and Thursdays or Tuesdays and Fridays.

An alternative to the 2-day/week regimen is splitting body parts that are exercised so that half are performed on 2 days while the other half is exercised on 2 other days. This may be more difficult when PRT is performed exclusively at the dialysis unit, but patients might be empowered to execute the fourth day at home. The current evidence-based exercise guidelines for people with CKD [17,18] recommend 2 nonconsecutive days/week for PRT.

Intensity (resistance)

Intensity metrics used in RT include percentages of the one-repetition maximum (1-RM, the maximal load that was successfully moved only one time during an initial assessment), a prescribed number of repetitions before exercise failure, for example, 10–15 repetitions maximum, and ratings of perceived exertion. RT intensity guidelines are similar for advanced CKD and chronic dialysis patients with only the number of repetitions at a particular intensity being different [17]. Recommendations for MHD patients include one set of 12–15 repetitions or until fatigue using 60%–70% 1-RM on dialysis or nondialysis days. Individuals with advanced CKD not receiving dialysis are advised to perform 10–15 repetitions with at 60%–70% 1-RM or until fatigue [17]. Intensity recommendations for older individuals with severe muscle weakness and low threshold for exertional fatigue suggest two sets of eight repetitions using 60% of 5-RM (the maximum amount of weight that can be moved five times only) focusing on leg exercises [18].

The 1-RM test is highly effort dependent [94] and includes some risk of injury although the risk is minimized when properly administered by trained and experienced professionals. It has been safely administered to healthy individuals without musculoskeletal limitations [198], to pulmonary disease patients [79], lower risk cardiac patients [114,115], and to MHD patients [199,200]. Testing for 1-RM is very time-consuming and requires periodic retesting following strength gains. Another option uses a resistance that can be successfully lifted for a given range of repetitions, that is, 10–15 repetitions per set. These should be done in good form without reaching complete muscle failure. A total of 10–15 repetitions is roughly equivalent to 65%–75% of 1-RM depending on the muscle group [110]. As training progresses, prescribed repetitions-maximum often decrease, for example, with increases in load, for example, 8–12 RM (70%–80% 1-RM). This method of repetitions to near failure is self-adjusting for progressing training loads as one becomes stronger. As a rule, when an individual is able to complete three consecutive training sessions with all prescribed repetitions, the load should be increased enough to maintain the prescription, for example, at 10–15-RM in good form to near failure.

An alternative approach makes use of subjective ratings of effort in which moderate exercise is equivalent to 5–6 on a 0–10 scale (0 = no movement) and high-intensity exercise at 7–8 on a 0–10 scale [101]. Borg scale RPEs have been used successfully in several trials of PRT in people with advanced CKD. Examples include moderate effort, RPE 11–15 [80,201] vigorous effort, RPE 15–17 [78] and RPE 6–10 in which 10 is "extremely hard" on a modified OMNI scale [100].

Duration (sets and repetitions)

As with most guidelines for healthy older adults and patient groups, it is recommended that exercise training should begin with a single set of exercises for each major muscle group with 10–15 repetitions per set. Assuming that it will take one minute to correctly execute a set of 10–15 repetitions (4–6 seconds for a repetition) and 2 minutes for rest between sets, one exercise for each major muscle group can be completed in 25–30 minutes. With adaptation a second set can be added. See next for additional progression guidelines.

Type

There are several forms of resistance that can be used for PRT. Simple elastic resistance (bands or tubes), weighted vests and ankle/wrist weights, dumbbell weights, kettleballs, and various machine weights are available. Newer resistance exercise equipment makes use of weighted bars and balls, weighted rubber tubes, and more. These forms of resistance can provide graduated resistance exercise starting at <1 pound.

Carrying out PRT in the dialysis chair may be advantageous. Cheema et al. described simple methods for conducting RT at the dialysis chair for all the major muscle groups [159]. Relatively inexpensive equipment, including dumbbells, ankle weights, and elastic bands/tubing, can be placed on a mobile cart and wheeled among patients. Bennett et al. have suggested that a specially built stack weight machine could be used at the dialysis chair for conducting lower extremity resistance exercise [202]. Another approach includes the use of weight machines before starting the dialysis procedure [77], although limitations of space in the dialysis unit and the cost of this equipment may preclude this option. On the positive side, the visibility of exercise equipment may be motivating to the dialysis patients. These types of equipment can also be used for interdialytic PRT, but the approach described by Cheema et al. could also be easily and inexpensively adapted for home use.

Rest interval

Rest intervals are often overlooked in guidelines for exercise training and are not infrequently left to the practitioner or individual to decide how to implement. For *resistance exercise*, rest intervals between sets are often guided by the training objective, health and fitness of the participant, and exercise training history. One minute rest bwteen sets would be appropriate for people beginning PRT. Current evidence-based guidelines for healthy adultssuggest 2-3 minutes for rest between sets in a regimen designed to improve strength. Shorter rest intervals may be used by more well-conditioned individuals particularly when the primary objective is muscle hypertrophy (45–60 seconds) or muscle endurance (15–30 seconds) [110]. Since most RT for all the major muscle groups is performed 2–3 days/week, ≥1 rest day should be given before exercising the same body part again.

Progression

Progression of exercise is the sine qua non in RT and can be achieved in many ways by providing overload in the form of increasing sets, resistance, and number of training days per body part. After adaptation, increasing the number of sets from one to two may be the first choice for MHD patients. If time is available, a third day of PRT could be added. Since increases in muscle size and muscle strength are important outcomes in advanced CKD, increasing the load so that some or all of the training sets reach a high level of effort is desirable. For example, high levels of effort would be represented by 15–17, (hard to very hard) on the Borg 6–20 scale, or 5–7 (strong to very strong) on the Borg 0–10 scale. Finally, specific muscle groups might be targeted for additional emphasis. Since the muscles of ambulation are important for upright physical activity, including gait speed, and other lower extremity functions, additional PRT for quadriceps, hamstrings, hip abductors and adductors, and triceps surae could be considered.

Guidelines: enhancing flexibility

Joint flexibility tends to decrease with age, but research shows that improvement in flexibility at any age can occur after as little as three to four sessions of regular 2–3 days/week stretching [203,204]. Improving range of motion of joints through regular stretching is a useful adjunct to PRT for improving postural stability and balance [205,206]. Despite commonly held views, current evidence suggests that stretching is unlikely to be effective in reducing or preventing injuries, low back pain or delayed muscle soreness [206]. One RCT in MHD patients examined the possible benefits of a modified yoga-based exercise program [81]. After 24 15- to 30-minute yoga sessions distributed over 12 weeks, patients exhibited significant improvements in pain intensity, fatigue, sleep disturbance, grip strength, plasma levels of urea, alkaline phosphatase, total cholesterol, erythrocytes, and hematocrit, as compared to controls. Compliance was reported to be good.

Frequency

Stretching is a low-intensity activity, thus conducting stretching activity >2–3 days/week is not likely to bring about negative consequences [207]. Daily stretching for those patients who could benefit from additional stretching sessions is acceptable and brings about greater gains. Stretching can be included, but should not solely comprise, the warm-up and/or cool-down phases of the training session. But providing dedicated time just for stretching is more likely to allow time to focus on this activity and to properly complete at least one good stretch for each of the major muscle–tendon groups.

Intensity

The intensity of the stretch is determined by whether the final position achieved during the stretch is painful. It is recommended that the final stretching position should feel “tight” or slightly uncomfortable, but no actual pain should be experienced.

Duration

As with healthy individuals, holding a static stretch either actively or passively for 10–60 seconds is recommended. A target of 60 seconds of total stretching time for each major muscle–tendon group should be eventually achieved.

Rest interval

Rest between exercises or between stretching sessions is less of a concern because of the low intensity of stretching, assuming that the individual does not stretch to the point of pain. If one performs two or more 30-second repetitions of a stretch for the same muscle group, the next set can begin as soon as the individual feels ready.

Progression

Progression in stretching includes increasing the duration of each stretch, adding additional stretching postures to individual muscle groups, and increasing frequency. Increasing intensity is not appropriate.

Guidelines: improving balance and stability

Neuromuscular training that includes balance and postural stability exercises has been only recently included in guidelines for exercise and physical activity in healthy adults [207]. Exercise and other strategies to improve balance are particularly beneficial in older persons to reduce the risk of and fear of falling [205]. MHD patients have a higher rate of falling and greater morbidity from falls than the general population [208,209]. Risk factors for falls include fatigue and muscle weakness, both of which are exacerbated following an HD session [210]. Muscle weakness is a contributor to balance deficits, and in community-dwelling older people, exercise training is effective in reducing the rate of falls and risk of fall-related fractures [211]. Although there are no specific guidelines for implementing balance/stability exercise, it is reasonable to consider balance exercises such as semitandem and tandem stands, one-legged stands, and especially more dynamic balance, coordination, and agility activities such as Tai Chi. Tai Chi has been extensively investigated, with several studies reporting its effects on improving balance, reducing falls [212,213], and improving motor control.

Kaesler et al. reported a novel, uncontrolled postural stability program that uses "Pilates-inspired" exercises [214]. Eight community-dwelling adults, aged 66–71 years, were assessed for static and dynamic postural sway using a validated sway meter. Physical function was measured with a four-part balance test, a TUG, and a single sit-to-stand test for time followed by a sit-to-stand test where the number of transitions was timed over 30 seconds. Subjects then completed 8 weeks of twice-weekly 40-minute conditioning sessions. Each session consisted of performing 12 exercises with 15 repetitions of each exercise. Details of the exercises are available [214]. Significant improvements were seen in postural sway and the TUG. This work is encouraging, but the small sample size and lack of controls suggest the need for a more scientifically rigorous study of this method.

Risks of exercise in the advanced CKD patient

There is a lack of specific reporting of adverse events associated with exercise training in advanced CKD patients [7]. However, for MHD patients, both intra- and interdialytic exercise training are generally thought to be safe as reported in systematic reviews [7,17,18,50]. In healthy exercising individuals the most common injuries experienced are musculoskeletal [215], and the most consistent association is between intensity and/or greater total volume of exercise over time and higher risks of injury. This is not surprising, since the total amount of exercise (volume) is the product of the intensity, duration, and frequency of exercise. For healthy and patient populations alike, injuries can be effectively mitigated by appropriate screening, warm-up, and progression in the components of the exercise prescription. In most MHD patients the risk–benefit ratio generally favors exercise [17,50]. Instruction in proper technique, breathing, adherence to the recommended program, and reporting untoward responses to members of the health-care team are important preventative strategies.

As with healthy individuals, musculoskeletal injuries are the most common risk in exercising CKD patients, but other risks, particularly of cardiac origin, are more serious and are most often seen with high-intensity exercise [7,216]. Patients with CKD often have underlying cardiac disease, thus increasing their vulnerability to exercise-induced adverse cardiovascular events. However, no negative hemodynamic effects have been reported with exercise during MHD, and in fact, systolic BP (SBP) stabilizes during such exercise [29]. The greatest exposure to exercise-induced cardiopulmonary stress occurs at peak exercise; but to date, there are no published reports of adverse cardiovascular events associated with exercise testing or training in MHD patients [156]. Nonetheless, it is not uncommon for MHD patients who have no history of coronary artery disease or ischemic heart disease and who volunteer for exercise training to be found to have electrocardiographic evidence of ischemic heart disease on stress testing. Thus advanced CKD patients must be evaluated carefully for ischemic heart disease both before they are allowed into an exercise training program and they participate in such a program.

About 45% of MHD patients are diabetic [217]. Consequently, serum glucose control during exercise may be of concern. Exercise during dialysis may prevent hypoglycemia since the dialysate glucose will serve as a form of a glycemic clamp, with serum glucose levels drifting toward the dialysate glucose concentration, which is usually about 100- to 200-mg glucose monohydrate/dL [156]. Nevertheless, monitoring of serum glucose levels is appropriate if the MHD patient is diabetic and is taking hypoglycemic medications. These individuals should learn to balance quality and quantity of food intake, insulin, and exercise intensity and duration.

Advanced CKD is often associated with decreased bone mass and changes in bone architecture. [218]. These changes may worsen as CKD progresses. Consequently, fracture risk is higher than in healthy individuals. Jamal et al. reported that increased fracture risk was associated with impaired muscle performance [118]. It is likely that the appropriate inauguration, progression, and type of exercise training will help to avoid fracture risk and perhaps reduce it [11]. Huang et al. have suggested that increased exercise time is positively associated with femoral neck and lumbar spine bone mineral density, and that exercise training is positively correlated with these measures, although these relationships did not reach statistical significance [11]. Spontaneous tendon ruptures have been reported in MHD patients [119] and tend to be associated with hyperparathyroidism and not with exercise. Only one trial has specifically studied exercise-induced injuries or adverse events [78] with no statistically significant differences between the resistance-trained group and inactive controls over the 12-week study. One older female MHD patient experienced a partial tear of the supraspinatus muscle in week 6 of exercise training, but she continued to train with lower extremity exercises [219]. Studies specifically examining the injury versus exercise dose−response relationship for various modes of exercise training in MHD patients are needed. As recommended in Heiwe's systematic review, future RCT should specifically examine the frequency and nature of injuries and adverse events with special consideration for the dose and type of exercise [7].

Barriers to overcome

MHD patients encounter significant impediments to maintaining a regular exercise program both within and outside the dialysis center [50,220−222]. Commonly reported barriers to participation include fatigue, transportation limitations [222,223], lack of encouragement [223], and low motivation [224]. The recently reported Network 11 study of physical activity in 1323 ESRD patients revealed that lack of motivation, fatigue, perception of being too sick, and no place to exercise or lack of exercise equipment were the most frequently cited barriers to participation in physical activity [225]. Lack of motivation, the most frequently reported perceived barrier to participation in exercise [224,226], has also been associated with less physical activity [221]. Barriers to conducting exercise training in the dialysis center have been reported [227]. Dialysis center staff may not encourage or facilitate the ability of patients to exercise before, during or after an HD session, because the staff is very busy with many demands on its time or there is concern about the risks of exercise or uncertainty regarding its benefits [24]. Dialysis staff also may be reluctant to encourage exercise among dialysis patients, because they believe it is not their responsibility to do so, and they usually do not have the skills to implement exercise training [224]. Probably of particular importance is that the dialysis staff and health-care worker to patient ratios in chronic dialysis units in the United States generally allow little time for dialysis staff to spend time on encouraging, assisting, and monitoring exercise training of patients.

Two studies have revealed that nephrologists typically do not counsel their patients regarding exercise, query physical activity or exercise habits, or provide guidelines for implementing exercise training [221,228,229]. Interestingly, while the vast majority of nephrologists agreed that exercise was potentially beneficial, the physicians surveyed thought that dialysis patients would not be interested in learning about exercise, were concerned about the risks of exercise, and believed their patients would not increase their physical activity even if counseled to do so [228]. Counter to these physician opinions, a separate study of patients receiving MHD indicated that they would increase physical activity if recommended by their physician [221]. A 2019 focus group study confirmed these findings by reporting that the lack of advice from kidney care providers regarding exercise was a significant barrier to participation, and that exercise interventions should include counseling and prescribing exercise by nephrologists [229].

These problems are compounded by lack of interest and lack of training on the part of nephrologists and dialysis center staff as well as lack of appropriate exercise equipment and space. The latter impediments have been overcome using simple, inexpensive cycle ergometers [31], and resistance exercise equipment [230]. Novel weight machines have also been developed for RT while the patient is situated in the dialysis chair [202].

Safety and contraindications for exercise

Smart et al. reported that exercise training conducted during the course of research on MHD patients is safe. No deaths were reported in over 28,000 patient-hours of exercise in the studies included in their systematic review [30]. However, since patients with advanced CKD have a greater prevalence of heart disease than is present in the general population [231], a CPXT with 12-lead ECG and BP monitoring would be indicated in all adult patients with advanced CKD, MHD, CPD, and kidney transplant patients prior to beginning exercise training. Relative and absolute contraindications for exercise are available from the American Heart Association [70] and the American College of Sports Medicine [95].

Hypertension is common in CKD with a prevalence approaching 70%–90% in MHD patients [11]. The American College of Sports Medicine suggests that a resting BP > 180/110 is a contraindication for exercise. Clinical judgment may, however, modify this guideline based on patient history, health status, BP responses to a particular dose of exercise, and the benefit-to-risk ratio. A recent metaanalysis reported nonsignificant differences in changes in both SBP and diastolic BP (DBP) after varying amounts of exercise training [11]. SMD (95% CI) were −0.17 (−0.41, 0.08) for SBP and −0.23 (−069, 0.24) for DBP. Patients with CKD should be educated about abnormal responses, symptoms, when to not exercise or to stop exercise and to report these finding to their health-care professional [252]. BP should be monitored often to ensure safety during exercise training. A particular concern for increased BP during exercise is evident during resistance exercise training if a participant holds their breath while straining to move a resistance, that is, the Valsalva maneuver. This is a safety risk that can be virtually eliminated by teaching proper breathing techniques during resistance exercise training. The simplest instruction is simply "keep breathing; don't hold your breath while exercising." Some exercise trainers suggest regulating the breathing so that the participant exhales normally while making the effort against a resistance and inhaling when the resistance is moved back to the starting position. Either approach will avoid a Valsalva maneuver.

As noted previously, fragility fractures and spontaneous tendon ruptures have been reported in advanced CKD and ESRD patients, primarily due to hyperparathyroidism. Care in selecting the resistance during PRT or strength testing will help to avoid these problems.

Exercise during dialysis can result in fluid and electrolyte shifts that may contribute to exercise intolerance and the possibility of hypotension associated with the dialysis procedure [155]. Careful observation of the participant is important and may result in recommending that the patient decrease the work rate or stop exercising entirely on that day. Exercising only during the first 90–120 minutes of the HD session will often avoid these problems [17,95].

Urgent need for development of renal rehabilitation programs

Over 35 years of research on exercise training coupled with the systematic reviews and metaanalyses of these studies provide compelling evidence of the substantial benefits to CKD patients who participate in regular exercise. Prescribed exercise doses have been expertly developed and are systematic and comprehensive (Table 51.1). Although these encouraging data suggest here is improved HRQoL and greater survival with exercise [232], it is an uncommon feature in the lifestyles of most MHD patients. Indeed, two recent surveys of chronic dialysis patients reported that only 13% [225] and 17% [222] of respondents achieved the commonly recommended guideline of 150 minutes/week of moderate-intensity exercise. One international study of 21,000 MHD patients reported that over half of those surveyed exercised 1 day or less/week (Fig. 51.2) [233]. The downward spiral of decreasing physical ability consequent to ESRD, and possibly to the chronic dialysis treatment itself, may lead to marked increases in a sedentary lifestyle that leads to further decrements in physical ability and performance. Unless broken, the spiral continues downward toward disability. Clearly, we must do more to remove barriers to exercise and encourage greater participation to target levels of exercise and beyond. There have been several calls to action [49,155,228,232,234–236] to increase the participation of MHD patients in regular exercise and the time for formal "renal rehabilitation" is never more present than now. Encouragingly, currently, there are enthusiastic people who are forming an Exercise in CKD Working Group in the United States [237]. Similar groups are established in Canada, Europe, and Australia. A major reorientation is needed in how to engage advanced CKD patients in physical activity and sustain that engagement. Evidence suggests that the nephrologist and related health-care staff are the individuals who are best positioned to effect this change.

Implications for practice

> The 2005 Clinical Practice Guidelines for Cardiovascular Disease in Dialysis Patients [138], suggested that "All dialysis patients should be counseled and regularly encouraged by nephrology and dialysis staff to increase their level of physical activity." (guideline 14.2); "The goal for activity should be for cardiovascular exercise at a moderate intensity for 30 minutes on most, if not all, days per week. Patients who are not currently physically active should start at very low levels and durations, and gradually progress to this recommended level." (Guideline 14.2.4.a.i)

> "Physical functioning assessment and encouragement for participation in physical activity should be part of the routine patient care plan. Regular review should include assessment of changes in activity and physical functioning." (Guideline 14.4.b.i)

These guidelines provide simple, valuable steps that all renal care practitioners can implement. Evidence-based guidelines for exercise training in CKD are available to the practitioner for endurance (Tables 51.5 and 51.6) and resistance exercise training (Table 51.7). These guidelines provide a basic framework for increasing participation in exercise and increased physical activity, but more detailed and comprehensive guidance is lacking. Given the low exercise tolerance of most advanced CKD patients, almost any increase in physical activity will be beneficial and should lead to progression in frequency, duration, and intensity of training and to enhanced benefits. The findings that low training loads and volumes have been shown to be capable of stimulating improvement [185] suggest a large adaptation window because of the significant debility of ESRD patients. The use of the AIDES method [238] shown in Table 51.8 may facilitate participant adherence to the exercise intervention.

Of clear importance is the need to remove barriers to participation in exercise training and physical activity as noted previously. There is a need to increase the nephrologist's knowledge base and willingness to educate his/her patients that regular exercise training may improve their walking capacity, physical fitness, and possibly overall health. Physicians should determine the activity level of patients and encourage them to reach the targets for the type, frequency, duration, and intensity of exercise outlined in this chapter. Real and perceived barriers to participation in regular exercise and physical activity should be investigated and addressed. Since maintaining an in-center exercise program falls largely on the clinical staff, their training and support are vital [222–224,229]. Engagement in regular exercise for the MHD patient might be better facilitated at the chronic dialysis center that has the potential advantages of equipment availability, supervision, and monitoring. However, regular exercise training can also be successful in outpatient supervised settings or in community-based programs [216]. Home exercise, including simple walking, is also useful in augmenting daily physical activity and for achieving the 150 minutes or greater per week physical activity target.

These are difficult tasks for many physicians who may not have the time, training, or desire to advise and monitor effective exercise training for their patients [222]. However, Painter [234] has suggested that even within the constraints of short patient visits, physicians can do the following:

- Ask the patient about physical activity, and help identify barriers to exercise and physical activity.
- Recommend increasing physical activity, if levels are low, by recommending walking when feasible and appropriate.
- Provide such educational materials as
    - "Exercise for the Dialysis Patient" available free from LifeOptions.org, a rehabilitation program dedicated to those with kidney disease.
    - "Getting Motivated to Exercise" available online from the National Kidney Foundation (United States) at https://www.kidney.org/news/monthly/Getting_Motivated_to_Exercise?homeslider = Option.
    - "Strategies for Improving the Effectiveness of Exercise in Dialysis Patients" American Kidney Fund by Kenneth Wilund, PhD. Available online as a slide presentation at https://www.kidneyfund.org/assets/pdf/training/exercise-training.pdf This presentation is also available as a YouTube video narrated by Dr. Wilund. https://www.youtube.com/watch?v = DFbOLhURpqY.
- Refer to a trained health-care professional who is qualified to work with exercise for patients with chronic disease, such as physical/occupational therapists, cardiac rehabilitation specialists, or clinical exercise physiologists.
- Referrals can then be regularly followed up during the routine clinic visits to assess participation and progress and to provide encouragement.

For the interested physician or health-care provider, help is available in the form of a national initiative sponsored by the American College of Sports Medicine called Exercise is Medicine. Shared with the American Medical Association, the guiding principles of Exercise is Medicine are designed to help improve the health and well-being of the nation through a regular physical activity prescription from doctors and other health-care providers. Many resources for physicians and

TABLE 51.8 Adaptation of the AIDES method [238] for improving adherence to exercise training and physical activity.

A:	Assessment (see Table 51.3)	Assess all components of health-related fitness and physical performance
I:	Individualization	Individualize the exercise training regimen
D:	Documentation	Provide written guidelines and progress monitoring
E:	Education	Provide accurate and continuing education tailored to the needs of the individual
S:	Supervision	Provide continuing supervision of the regimen

health-care workers are available through Exercise is Medicine and include Exercise is Medicine Health Care Providers' Action Guide, Exercise is Medicine Action and Promotion Guide, Billing and Coding for Physical Activity Counseling, ACSM's Exercise is Medicine: A Clinician's Guide to Exercise, and National Center on Physical Activity and Disability brochure for Health Care Providers. Detailed information is available at https://exerciseismedicine.org/physicians.htm.

Assistance is also available from American College of Sports Medicine Clinical Exercise Physiologists. These allied health professionals are trained and certified to assess, design, and implement exercise/fitness programs and provide education and counseling for individuals with chronic health conditions (e.g., heart disease, diabetes, cancer, lung disease, and renal disease). As such, they would be valuable members of the renal rehabilitation team.

Summary

This chapter has sought to provide physicians and other related health-care providers with a summary of current evidence for the value of comprehensive exercise training and increased physical activity for the patient with CKD. Basic principles underlying exercise training are reviewed, and specific methods for assessing health-related fitness and physical function in CKD patients are presented. The common elements that guide exercise training program design for endurance and resistance exercise, flexibility, and stability are presented along with specific applications for CKD patients. Sufficient detail is provided to guide clinical practitioners toward implementing exercise training programs for their patients. Some of the predominant barriers to participation are identified along with risks and safety for exercise training in CKD.

More data on exercise training efficacy in people with CKD stage 2–4, CPD patients, and renal transplant recipients are needed with careful research design and adherence to guidelines that guide high-quality studies. There are presently little to no data on the long-term effectiveness of exercise training in people with any stage of CKD. Properly administered exercise training has been shown to be of great short-term benefit, but we do not know whether the improvements are sustainable.

Finally, a renewed call to action is expressed in conjunction with the implications for implementation of exercise training programs for patients with CKD. There is an urgent need for physicians and associated staff who work with CKD patients to regularly inform them of the value of physical activity, assess current physical activity and physical function status, and moderate barriers to participation. These health-care workers should encourage regular exercise and increased physical activity and ensure that the appropriate intensity, duration, and frequency of exercise are added to the treatment plan. Resources for physicians and health-care practitioners for increasing knowledge and skills in exercise prescription and training for patients are provided. We can expect to see advances in evidence-based exercise training guidelines for CKD patients as research continues to elucidate specific applications of the FITT principle.

There are clear-cut benefits for improved performance and physical function awaiting patients who regularly exercise. A sea change is needed in the manner in which patients with CKD engage in physical activity, and evidence suggests that the nephrologist and his/her associated staff are the individuals who are best positioned to effect this change. The time for formal "renal rehabilitation" is never more present.

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CHAPTER

52

Anabolic and anticatabolic agents in kidney disease and kidney failure

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Introduction

Chronic kidney disease (CKD), and particularly end-stage renal disease (ESRD), is associated with muscle wasting that contributes to muscle weakness, poor physical function, and increased mortality [1]. Many factors related to CKD and ESRD, such as inflammation, poor nutrition, chronic uremia, and androgen deficiency converge on pathways regulating muscle mass to drive catabolism, inhibit anabolism, or both. Thus multiple therapeutic targets in these pathways have been studied in the hope of preventing, decreasing, or mitigating muscle wasting and even increasing muscle strength and physical function in those with CKD and ESRD. This chapter will review and discuss many of these therapeutic targets that have been investigated in clinical trials recently and over the preceding decade (Fig. 52.1).

Skeletal muscle is composed of multinucleated muscle fibers containing organized units of contractile elements. Muscle contraction is the result of ATP-dependent interactions between hundreds of myosin and actin filaments in each sarcomere, which are then amplified by thousands of sarcomeres in each muscle fiber. A specialized endoplasmic reticulum (sarcoplasmic reticulum) stores calcium and allows for rapid conversion of electrical potential from a nerve impulse to a chemical signal to initiate contraction. Skeletal muscle contraction is highly adaptive to increased demand in response to exercise or load bearing. In addition, as a major protein store in the body, skeletal muscle can also respond to the metabolic activity that maintains whole-body protein homeostasis. Thus skeletal muscle can participate in several anabolic and catabolic processes that increase or decrease in muscle mass. Muscle homeostasis is a carefully regulated balance between these anabolic and catabolic pathways and the cellular signaling that controls these processes.

The rate of whole-body protein turnover in a normal, healthy man is approximately 3.7–4.7 g of protein/kg/day, most of which are intracellular proteins [2]. The half-lives of proteins and rates of proteolysis are tightly regulated. The rate of protein turnover increases acutely in states of anorexia (starvation), inflammation, and infection, with preferential loss from the skeletal muscle such that the muscle–protein balance becomes negative, but visceral organ function is relatively preserved. Much of the amino acids released from breakdown of protein are then used for gluconeogenesis or by muscle for energy production [2]. Over time, even in the continued presence of the above disorders, protein breakdown diminishes substantially, which can be considered an adaptive response.

Anabolic mechanisms and pathways

Mononucleated myogenic stem cells called satellite cells reside between the sarcolemma and the basal lamina in the muscle fiber and are normally quiescent in skeletal muscle of adults. However, in the setting of muscle injury, satellite cells are able to proliferate and fuse with each other and with damaged muscle fibers, contributing myonuclei to growing muscle fibers to regenerate skeletal muscle. Although satellite cells can form new satellite cells to self-replenish, their numbers decrease with age [3].

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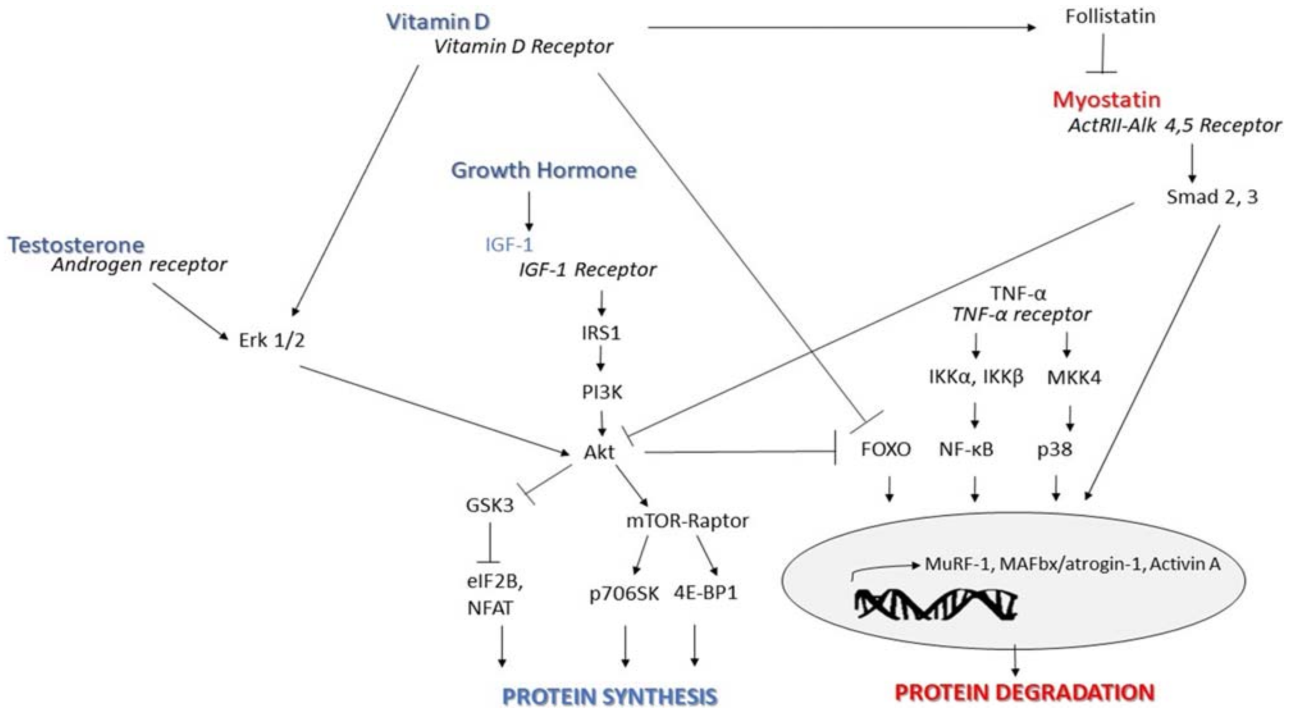

FIGURE 52.1 Major anabolic and catabolic pathways for protein that could be targeted for therapeutics.

Several molecular pathways contribute to skeletal muscle hypertrophy and regeneration. The insulin-like growth factor-1 (IGF-1)/PI3K/Akt pathway is one of the best described pathways in skeletal muscle anabolism. IGF-1 binds to its receptor (IFG1-R), which induces phosphorylation of the receptor and then recruitment of insulin receptor substrate 1 (IRS1). Subsequent stimulation of the PI3K/Akt pathway results in phosphorylation and activation of mTOR signaling. mTOR signaling translates downstream to enhance translation initiation and protein synthesis. In mouse models, activation of the Akt pathway induces muscle hypertrophy and increases skeletal muscle mass [4]. Testosterone, growth hormone (GH), and vitamin D have all been considered as potential therapeutic agents to stimulate this anabolic pathway to increase muscle mass and function (Fig. 52.1). This pathway can be inactivated when IRS1 is tagged for ubiquitin-mediated degradation by ligases such as SOCS1 and SOCS3, a link between the anabolic and catabolic pathways in muscle.

Catabolic mechanisms and pathways

Muscle protein catabolism is a normal and routine process, and muscle wasting occurs when there is a shift such that protein degradation and proteolysis exceeds protein synthesis. The major proteolytic pathway is through activation of capase-3 and the ubiquitin−proteasome system (UPS) (see also Chapter 10: Metabolic and Nutritional Responses to Acidemia and Alkalemia). Ubiquitin is activated by an enzyme (E1), transferred to carrier proteins (E2), and then conjugated to the substrate protein to be degraded by a ligase (E3). This then leads to rapid degradation of the substrate protein by a proteasome [2]. Catabolism can either be triggered by catabolic signaling such as through the myostatin pathway or by a decrease in anabolic signaling. Decreased anabolic signaling through phosphorylated Akt also leads to the downstream stimulation of specific E3 ubiquitin-conjugating enzymes: atrogin-1/muscle atrophy F-box (MAFbx) and muscle ring finger 1 (MuRF1). These enzymes recognize specific muscle proteins such as myosin heavy chain and myosin-binding protein C in the sarcomere, increasing their degradation by the UPS. Myostatin negatively regulates Akt signaling and induces signaling in the MuRGF1 and MAFbx pathways that results in increased catabolism.

This chapter will review major agents acting directly on muscle anabolic or catabolic pathways that have been tested in clinical trials with outcomes related to muscle mass or muscle function. However, it is important to note that there are other strategies that might affect these pathways indirectly, such as interventions to address nutrition and inflammation. Future therapeutic approaches may also involve mechanisms involving pathways independent of classic anabolic signaling, such as targeting G-proteins, mitochondrial oxidative metabolic pathways, and muscle-specific microRNAs.

Myostatin

Myostatin, a member of the transforming growth factor-β (TGF-β) superfamily, has long been known to be an important negative regulator in skeletal muscle. The myostatin story started well before the discovery of the responsible gene, with its origin in selective cattle breeding. In 1807 a British farmer described "bovine muscular hypertrophy" in cattle with such excessive muscles they were dubbed "double muscled." In 1997 McPherron et al. showed that muscle isolated from myostatin knockout mice weighed two to three times more than those isolated from wild-type mice. The skeletal muscle increase appeared to be mostly muscle hyperplasia with some muscle fiber hypertrophy [5]. McPherron and Lee went on to show that mutations in the myostatin coding sequence are responsible for muscle hypertrophy in the Belgian Blue and Piedmontese breeds of double-muscled cattle [6]. Myostatin is highly conserved across species, including in pigs, chickens, turkeys, baboons, and humans [6]. The importance of the myostatin gene in humans was highlighted by a case report of an infant with muscular hypertrophy. At 6 days of age the infant's quadriceps muscle volume by ultrasound was 7.2 SD above the mean for age- and sex-matched controls. When he was 4.5 years old, the child was able to hold two 3-kg dumbbells in horizontal suspension with arms extended. This child was found to have a loss of function mutation in myostatin resulting in absence of serum myostatin propeptide [7]. Conversely, myostatin overexpression in mice leads to loss of muscle parenchyma and fat analogous to cachexia without change in nutritional intake [8].

Myostatin is first expressed as a 375-amino acid propeptide, which is then cleaved to form a latent myostatin and further processed to produce a 26-kDa active myostatin. Myostatin binds to activin receptor type IIB (ActRIIB) and with lesser affinity to activin receptor type IIA, forming a complex with the activin type I receptors (ALK 4/5). Activation of these receptors further activates SMAD2 and SMAD3 transcription factors. This leads to downstream signaling that suppresses Akt signaling and increases expression of atrogin-1 and MuRF1. These actions, in turn, enhance protein degradation by stimulating ubiquitin–proteasome activity [9]. Follistatin is a glycoprotein that binds to myostatin and inhibits binding to its receptor. Follistatin also blocks activities of other TGF- β family members that limit muscle mass, such as activin A [10].

Plasma myostatin concentrations appear to be higher in individuals with CKD compared to those without CKD, even in stages 1 and 2 CKD, and there is an inverse correlation between myostatin concentrations and eGFR [11]. Muscle biopsies obtained from patients with stage 5 CKD at the time of catheter insertion for peritoneal dialysis showed apoptotic loss of myonuclei, upregulated expression of myostatin and IL-6, and decreased expression of IGF-1 compared to controls. In addition, upregulation of myostatin was associated with increased IL-6 expression, suggesting a pathway by which inflammation may lead to protein catabolism and reduction of muscle mass [12]. In mouse models of CKD, injection of antimyostatin antibodies prevented the development of muscle atrophy and reversed established muscle atrophy. These outcomes occurred through suppression of inflammatory cytokines, reduction in protein degradation, increase in satellite cell function, and increase in IGF-1 signaling [13].

Myostatin inhibition is a logical target for human therapeutics to counter loss of muscle mass in CKD. However, despite the excitement surrounding preclinical data on myostatin inhibition, clinical trials of myostatin inhibitors have been met with many difficulties. Current strategies to block myostatin largely focus on using antibodies to block myostatin or its receptors, ligand traps to block myostatin from its receptor, or overexpression of follistatin as a natural inhibitor of myostatin. Here, we describe several prominent therapeutics to block myostatin or TGF-β family signaling that have been evaluated in clinical trials (Table 52.1).

Antimyostatin therapeutics (antibody, peptibody, or adnectin)

MYO-029 (Wyeth) was the first monoclonal antimyostatin antibody to be tested in clinical trials in humans. Although this myostatin inhibitor increased muscle mass in phase I/II trials, timed muscle testing did not improve significantly, leading to discontinuation of development of this drug. LY2495655 (Lilly) is a human monoclonal antibody against myostatin. A phase II trial in patients with cancer cachexia was terminated due to a higher death rate in the group receiving LY2495655, and another trial among patients undergoing elective arthroplasty did not meet its efficacy endpoints [14,15]. However, a study in elderly individuals with a history of falling showed that LY2495655 increased appendicular lean body mass and improved stair-climbing time, muscle power, chair rise times, and gait speed compared to the group that

TABLE 52.1 Antimyostatin therapeutics.

Drug molecule	Mechanism	Study population	Trial stage	Note
Stamulumab; MYO-029 (Wyeth)	Myostatin Ab	Muscular dystrophy	Phase II	Discontinued; failed to increase muscle strength
PF-06252616 (Pfizer)	Myostatin Ab	DMD	Phase II	Did not meet efficacy endpoints
		LGMD2I	Phase II	
Trevogrumab; REGN1033 (Regeneron)	Myostatin Ab	Sarcopenia	Phase II	
REGN1033 + REGN 2477 (garetosmab)	REGN2477: activin A, Ab	Postmenopausal women, healthy men	Phase I	Trial in progress
Landogrozumab; LY2495655 (Lilly)	Myostatin Ab	Pancreatic cancer	Phase II	Terminated due to imbalance in death rate between treatment arms
		Elderly faller	Phase II	
		Elective total hip arthroplasty	Phase II	Did not reach threshold of primary objective
PINTA-745; AMG 745 (Amgen)	Antimyostatin peptibody	End-stage renal disease	Phase II	Discontinued, due to not meeting efficacy endpoints
BMS-986089 (Bristol–Myers–Squibb)	Antimyostatin adnectin	DMD	Phase I/II	
Ramatercept ACE-031 (Acceleron)	Soluble activin type IIB R	Postmenopausal women	Phase I	Completed in 2011
		DMD	Phase I	Terminated; due to gum bleeding, nose bleed, and small dilated vessels in skin
ACE-083 (Acceleron)	Modified human follistatin, "ligand trap"	FSHD	Phase II	
		Charcot–Marie–Tooth disease	Phase II	
Bimagrumab (BYM338) (Novartis)	ActRIIA/ActRIIB Ab	sIBM	Phase IIb/III	Did not meet primary endpoints
		Sarcopenia	Phase II	Completed 2013
		Hip fracture	Phase II	
		COPD	Phase II	
		Lung and pancreatic cancer	Phase II	
AAV1.CMV.huFS344	Delivery of follistatin	BMD and sIBM	Phase 1/IIa	
AAV1.CMV.huFS344	Delivery of follistatin	DMD	Phase I/II	

Ab, Antibody; *ActRIIA*, activin receptor type IIA; *ActRIIB*, activin receptor type IIB; *BMD*, Becker muscular dystrophy; *COPD*, chronic obstructive pulmonary disease; *DMD*, Duchenne muscular dystrophy; *FSHD*, facioscalpulohumeral muscular dystrophy; *LGMD2I*, limb–girdle muscular dystrophy 2I; *sIBM*, sporadic inclusion body myositis.

received placebo [16]. There has been only one drug in clinical trials of patients with ESRD. The drug tested was PINTA 745 (Atara Bio), a myostatin-neutralizing peptide fused to an Fc domain (a myostatin peptibody). Unfortunately, development was discontinued after PINTA 745 failed to meet its efficacy endpoints in phase I/II trials [17]. A myostatin antibody, REGN1033 (Regeneron), has been evaluated for patients with sarcopenia. PF-06252616 (Pfizer) has been in phase II clinical trials in patients with Duchenne muscular dystrophy (DMD) and limb–girdle muscular dystrophy 2I. However, further trials in patients with DMD were terminated after the phase II trial failed to meet its primary efficacy endpoints. Bristol–Myers–Squibb developed an engineered protein designed to bind with high affinity and specificity to myostatin, an anti-myostatin adnectin (BMS-986089), which is currently in phase II/III trials in ambulatory boys with DMD. Adnectins are engineered to be similar to antibodies but are more stable and easier to produce [18].

There are several potential reasons why myostatin inhibitors have not produced expected outcomes in clinical trials. Several ligands in the TGF-β superfamily other than myostatin also participate in the signaling pathway leading to inhibition of skeletal muscle anabolism and increasing catabolism, most notably activins. Activin A appears to have a more prominent role in muscle inhibition in primates than in mice, which may help to explain why pure myostatin inhibition produces less response in human clinical trials than in preclinical trials in mice [19]. Preferentially, inhibiting signaling by myostatin may also prime the muscle to respond maximally to activation of SMAD2/3 signaling from other TGF-β superfamily ligands, such as activins [20]. In support of this explanation, simultaneous inhibition of myostatin and activins appears to lead to a synergistic hypertrophic response [21]. As a consequence, newer drugs in development, which are described next, block multiple targets or more downstream targets of myostatin signaling.

Activin A-based therapy

REGN2477 (Regeneron), an antibody against activin A, is combined with a myostatin blocker (REGN1033), and it is hypothesized that this combination might synergistically block two major ligands in the signaling pathway through the ActIIRB receptor. This combination approach is currently in phase I clinical trials in postmenopausal women and healthy adult men [22].

Ligand trapping (soluble ActRIIB or follistatin based)

ACE-031 is a recombinant protein that contains part of the ActRIIB receptor fused to part of a human antibody. The result is a soluble, circulating form of ActRIIB that can interfere with myostatin binding to the endogenous ActRIIB receptor. The development of this drug was halted due to safety concerns related to epistaxis and telangiectasias that were observed in a phase II trial in patients with DMD [23]. The same company, Acceleron, has two newer drugs in clinical trials, ACE-083 and ACE-2494, that are a fusion of a version of human follistatin with an IgG Fc domain. This follistatin fusion protein binds tightly to myostatin and activins so as to “trap” these ligands and neutralize their ability to signal downstream [24].

ActRIIB binding

A different strategy adopted by Novartis is to target the receptor in the TGF-β pathway rather than such ligands as myostatin and activins. Bimagrumab is a human monoclonal antibody that binds ActRIIB, thereby preventing binding of myostatin with several TGF-β family ligands. Novartis conducted several clinical trials of patients with sarcopenia, chronic obstructive pulmonary disease (Type 2 DM), sporadic inclusion body myositis (sIBM), hip fracture surgery, or cancer cachexia (lung or pancreatic). In the phase II trial among community-dwelling adults with sarcopenia, bimagrumab increased lean body mass and thigh muscle volume. In addition, the participants who received bimagrumab demonstrated improvement in grip strength, gait speed, and 6-minute walk time as compared to those receiving placebo [25].

Follistatin overexpression

Follistatin is not only a potent myostatin inhibitor, but also it manipulates TGF-β signaling pathways independent of its action on myostatin [26]. Using a novel approach of delivering follistatin via an adeno-associated virus vehicle, investigators have completed small proof-of-concept clinical trials in patients with Becker muscular dystrophy and sIBM with positive results. This has set the stage for larger pilot trials of follistatin delivery.

Current clinical trials continue to focus on blocking TGF-β family ligands, but this approach faces several challenges. The specificity of the drug candidates has been difficult to achieve given the high degree of similarity among receptors of TGF-β family members. Pharmaceutical inhibition of myostatin has led to muscle hypertrophy [27], whereas hyperplasia is the mechanism by which muscle size increases in myostatin knockout models, and this may be one reason several clinical trials have achieved increases in muscle mass without improvement in muscle function. Also, several clinical trials have been conducted in people with chronic neuromuscular diseases; an increase in their muscle mass without the appropriate increase in innervation of these muscles may limit the improvement in muscle function. More clinical trials of CKD and ESRD patients are needed to examine whether these same problems impair drug effectiveness in these populations.

Currently, most antimyostatin antibodies have targeted the mature form of myostatin. However, newer strategies are focusing on promyostatin and latent myostatin. These proteins may be more specific and may have a more durable effect, since latent myostatin is the predominant form of myostatin in circulation, and promyostatin is the predominant form in the muscle. Antibodies targeting promyostatin are still in preclinical phases of investigation at this time [28].

GH and IGF-1

GH is secreted in a pulsatile fashion from the pituitary gland in response to signaling from GH-releasing hormone. This release is inhibited by somatostatin. Other nutritional hormones such as insulin and ghrelin also play a role in regulating GH release. Most of the anabolic actions of GH are related to the stimulation of IGF-1. IGF-1 is a 70-amino acid peptide produced in the liver and locally in GH-stimulated tissues. In circulation, IGF-1 is largely protein bound to IGF-binding proteins (IGFBP-1–6) and especially to IGFBP-3. IGF-1 signaling is important in skeletal muscle homeostasis since it activates anabolic signals and inhibits catabolic signals by activating the PI3K/Akt pathway (Fig. 52.1). IGF-1 also inhibits muscle catabolism by inhibiting expression of MuRF1 and Atrogin-1 [29]. In adult mice a decrease in IGF-1 signaling leads to a decrease in anabolic signals but to no change in catabolic signals, tilting the balance toward muscle atrophy [29]. Conversely, overexpression of IGF-1 in mouse skeletal muscle leads to myofiber hypertrophy [30].

GH also has direct, rapid onset effects on protein metabolism. The mechanisms of these actions are less well understood; however, the rapidity of these metabolic actions suggests that they are independent of signaling through IGF-1. It is thought that one of the direct actions of GH on tissue is to stimulate incorporation of amino acids into protein [31]. In one study, rodents that have undergone hypophysectomy undergo a loss in type I and type II muscle fibers. Replacement of GH reverses this loss of muscle fiber [32,33]. There are also opposing data showing no change in muscle fibers with GH replacement [34].

GH has long been used as an anabolic and performance-enhancing agent in competitive sports in humans. However, until the 1990s, there were limited data from clinical trials supporting its effectiveness. In one of the trials establishing GH as an anabolic hormone, 12 men with hypopituitarism treated with GH for 6 weeks showed increases in whole-body protein synthesis [35]. GH was also shown to counteract corticosteroid-induced protein catabolism [36]. These results were confirmed in adults with GH deficiency [37]. However, this increase in protein synthesis did not always translate into increases in muscle fiber area [38–40]. GH may also improve muscle function in other ways, such as by increasing aerobic exercise capacity by increasing red cell mass and thereby increasing oxygen delivery to muscle [41–43]. In a clinical trial in older healthy adults, participants who were 61–81 years old were randomized to receive placebo or biosynthetic GH injections three times a week for 6 months. Those who received GH showed an increase of 3.7 kg (0.7–6.6 kg) in lean body mass [44]. However, despite the increase in lean body mass, a subsequent study did not show that GH improved physical function as measured by knee or hand-grip strength [45].

CKD has been described as a state of GH resistance rather than deficiency, which complicates efforts to restore the GH axis because higher doses of exogenous GH would be needed. There are several possible mechanisms leading to a disturbed GH/IGF-1 axis in renal failure. Most investigators have found normal serum IGF-1 levels in individuals with CKD, perhaps due to decreased clearance of GH combined with increased feedback at the pituitary. However, observations that hepatic GH receptor gene expression is lower in chronically uremic states than among healthy individuals [46] suggest GH resistance. Also, IGF-binding protein concentrations are increased in CKD, limiting the bioavailability of circulating IGF-1 [47]. Finally, uremic rats treated with IGF-1 demonstrated less response as measured by increase in protein synthesis and decrease in protein catabolism as compared with control rats, suggesting IGF-1 resistance in CKD [48]. IGF-1 is not removed during hemodialysis because of its size and the fact that it is largely protein bound.

There have been small clinical trials in chronic dialysis patients examining the use of recombinant GH or IGF-1. In an early study in six maintenance hemodialysis (MHD) patients, recombinant human GH (rhGH) was administered for 6 weeks in a crossover study. The authors showed that rhGH administration led to an increase in muscle protein synthesis and a decrease in negative muscle protein balance as measured by phenylalanine balance [49]. Another trial randomized 21 MHD patients in Denmark to treatment with GH for 6 months versus placebo. The authors found that in the GH treated group, lean body mass as measured by DEXA increased by 3.0 ± 0.75 kg compared to 1.03 ± 0.45 kg in the placebo group [50]. The largest clinical trial designed to investigate whether GH improves muscle mass and strength among MHD patients was The Effect of Somatropin Treatment in Adult Patients on Chronic Dialysis (OPPORTUNITY) trial. Investigators had planned to enroll 2500 patients randomized to placebo or injections of recombinant GH for a duration of 24 months, but unfortunately, the trial was terminated early due to slow recruitment, and the patients who were recruited were followed for a shorter period of time, resulting in lower statistical power. There was no detectable change in lean body mass or exercise capacity comparing those who received GH with those who received placebo. There was, however, a decrease in total body fat and hs-CRP in those receiving GH [51].

In light of this experience, the future use of GH to stimulate anabolic effects in CKD is uncertain. Barriers include the short half-life of GH and IGF-1 and continuing uncertainty about their efficacy. Sustained-release formulations of both rhGH and IGF-1 have been tested in clinical trials among GH-deficient pediatric patients, but they have not been studied in patients with CKD. A concern of these longer lasting preparations is that clearance of GH is already reduced in the setting of CKD. Recombinant IGF-1 injections have been tested in patients with neuromuscular diseases, but results from these trials have been disappointing, showing a lack of change in muscle volume [52] and muscle function [53]. There are also lingering concerns about potential adverse effects of GH on cardiovascular risk. Patients with acromegaly from chronic excess GH exposure are at risk for hypertension, ventricular hypertrophy, cardiac valve disease, arterial intima-media thickness, and arrhythmias.

Data supporting caution with the use of therapeutic GH come from a published study with data from two randomized multicenter placebo-controlled trials conducted in parallel in Europe. Patients in the intensive care unit were randomized to rhGH or placebo, and although the patients treated with rhGH had improved nitrogen balance, hand-grip strength was unaffected. In addition, patients treated with rhGH had a higher mortality rate and longer hospitalization compared to those in the placebo group [54]. These studies were done in critically ill populations and may not be generalizable to those who are less ill. Furthermore, the reason for increased morbidity and mortality in this study is still unclear. Possible mechanisms include fluid retention, hyperglycemia, and higher rhGH dosing due to patients being in a hypercatabolic and GH-resistant state, and these mechanisms are potentially relevant in determining a therapeutic window for GH use in CKD.

Finally, other promising methods for increasing the bioavailability of IGF-1 are emerging and may be promising in states of GH resistance such as CKD. These include the use of small molecules to block IGF-1 from binding to its binding proteins or to displace it from binding proteins once bound. The development of these molecules is currently limited to preclinical trials.

Vitamin D

Vitamin D was discovered in 1919 by Sir Edward Mellanby, who induced rickets in dogs that were kept indoors. He noticed that rickets was cured with cod liver oil and thought the effect was due to vitamin A. However, in 1922, it was discovered that cod liver oil treated by heat to destroy vitamin A still cured rickets, and thus another substance must be responsible. The new substance was named with the next available letter in the alphabet and called “vitamin D” [55,56].

The formation of vitamin D begins in the skin where UV radiation drives the conversion of 7-dehydrocholesterol to cholecalciferol (vitamin D3). Vitamin D3 circulates largely bound to vitamin D−binding protein and is transported to the liver where 25-hydroxyvitamin D (25OHD) is generated. 25OHD next undergoes 1 α-hydroxylation in the proximal tubules of the kidney, which is the rate-limiting step in the synthesis of the most active form of vitamin D, 1,25-dihydroxycholecalciferol (1,25-$(OH)_2D$) [57] (Fig. 52.2). Finally, 1,25-$(OH)_2D$ is inactivated by 24-hydroxylase, an enzyme that also converts 25OHD to 24,25$(OH)_2D$, an inactive metabolite. Several molecules and hormones interact in the regulation of 1 α-hydroxylase activity to synthesize active vitamin D, including calcium, parathyroid hormone, calcitonin, GH, IGF-1, and fibroblast growth factor-23 (FGF-23) [58] (please also see Chapters 23, 24, and 25).

Mechanism of vitamin D action in muscle

The influence of vitamin D on calcium, phosphorus and the maintenance of normal skeletal development has long been established. Vitamin D also affects skeletal muscle at the cellular level. 1,25-$(OH)_2D$ binds to the vitamin D receptor (VDR), which then binds to the nuclear receptor retinoid X receptors (RXRs) to modify gene transcription. These genomic effects are thought to increase expression of contractile proteins and myogenic transcription factors and to enhance differentiation of myoblasts into myotubes [57,59,60]. The nongenomic response to vitamin D involves activation of multiple cell signaling pathways, including cyclic adenosine monophosphate, protein kinase A, protein kinase C, protein kinase B/Akt, and extracellular signal−regulated kinase (ERK1/2). These pathways lead to rapid calcium influx into myocytes. This calcium signaling plays a role in myocyte contractile function by regulating muscle contractile proteins such as actin, myosin, and troponin C [57] (Fig. 52.3). In addition, vitamin D influences myocyte proliferation and differentiation [61], in part by influencing the fate of mesenchymal stem cells to promote myogenesis and inhibit fibrosis [62]. In vivo data in rats also suggest that vitamin D increases muscle cell proliferation and decreases apoptosis after trauma [63].

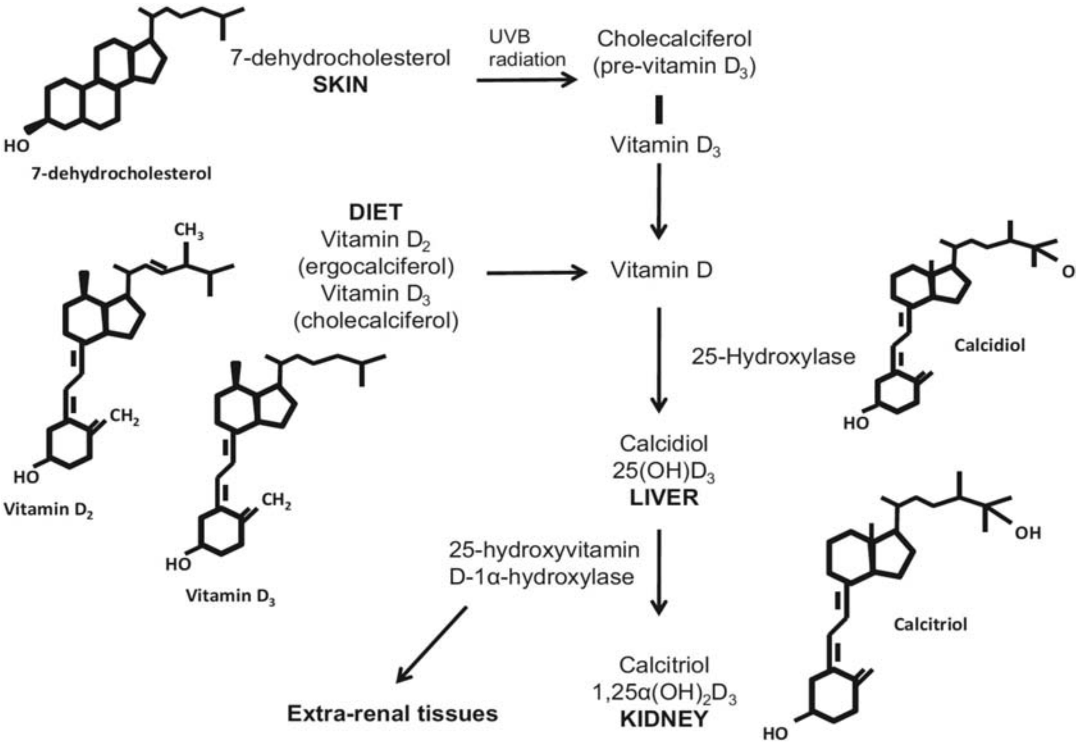
7-dehydrocholesterol
SKIN
HO
7-dehydrocholesterol
UVB radiation
Cholecalciferol (pre-vitamin D3)
Vitamin D3
DIET
Vitamin D2 (ergocalciferol)
Vitamin D3 (cholecalciferol)
Vitamin D
CH3
CH2
HO
Vitamin D2
CH2
HO
Vitamin D3
25-Hydroxylase
OH
Calcidiol
HO
Calcidiol
25(OH)D3
LIVER
25-hydroxyvitamin D-1α-hydroxylase
Extra-renal tissues
Calcitriol
1,25α(OH)2D3
KIDNEY
OH
Calcitriol
HO

FIGURE 52.2 Synthesis and metabolism of vitamin D. *Adapted from Dirks-Naylor AJ, Lennon-Edwards S. The effects of vitamin D on skeletal muscle function and cellular signaling. J Steroid Biochem Mol Biol 2011;125(3–5):159–168.*

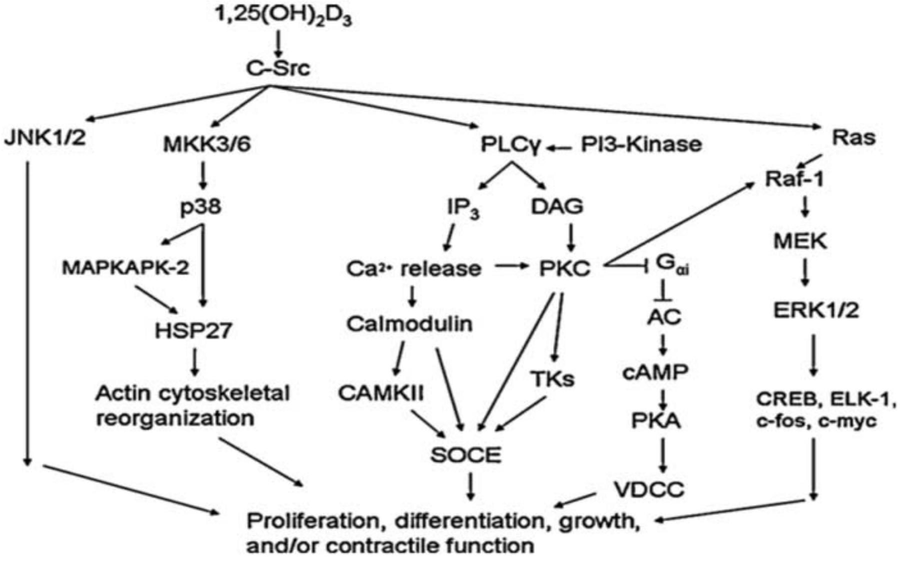
1,25(OH)2D3
C-Src
JNK1/2
MKK3/6
PLCγ
PI3-Kinase
Ras
Raf-1
p38
IP3
DAG
MEK
MAPKAPK-2
Ca2+ release
PKC
Gαi
HSP27
Calmodulin
AC
ERK1/2
Actin cytoskeletal reorganization
CAMKII
TKs
cAMP
CREB, ELK-1, c-fos, c-myc
PKA
SOCE
VDCC
Proliferation, differentiation, growth, and/or contractile function

FIGURE 52.3 Potential nongenomic effects of vitamin D in skeletal muscle. *AC*, Adenylyl cyclase; *CAMKII*, Ca^{2+}/calmodulin-dependent protein kinase II; *cAMP*, cyclic adenosine monophosphate; *CREB*, cAMP response element–binding protein; *C-Src*, proto-oncogene cellular Src; *DAG*, diacylglycerol; *ELK*, ETS like-1 protein; *ERK*, extracellular signal–regulated kinase; *HSP*, heat shock protein; *IP3*, inositol triphosphate; *JNK*, c-Jun N-terminal kinase; *MAPKAPK2*, mitogen-activated protein kinase–activated protein kinase 2; *MEK*, MAPK/ERK kinase; *MKK3/6*, mitogen-activated protein kinase kinase 3/6; *PKA*, protein kinase A; *PKC*, protein kinase C; *PLC*, phospholipase C; *SOCE*, store-operated calcium entry; *TK*, tyrosine kinase; *VDCC*, voltage-gated calcium channels. *Adapted from Dirks-Naylor AJ, Lennon-Edwards S. The effects of vitamin D on skeletal muscle function and cellular signaling. J Steroid Biochem Mol Biol 2011;125(3–5):159–168.*

Vitamin D deficiency and muscle function

VDR knockout mice develop atrophy of muscle fibers leading to significant impairment in motor performance [64]. There has been intense debate for many years over whether the VDR is expressed in human skeletal muscle; however, most experts now agree that VDR is expressed in skeletal muscle, albeit at very low levels [60,65,66]. Supporting the role of VDR in muscle is the observation that muscle atrophy is observed in individuals with VDR mutations even before they develop osteomalacia [67,68].

Clinical trials in the general population

Human rickets and osteomalacia have long been characterized by muscle weakness, particularly in proximal muscles [69]. Based on long-term observations of an association between myopathy and osteomalacia, there has been considerable interest in whether vitamin D supplementation could improve muscle strength and function. In older adults with sarcopenia, supplementation with 800 IU vitamin D and whey protein led to improvement in muscle mass and lower limb function [70]. In another randomized trial in older women with a baseline 25OHD level under 60 nmol/L (24 ng/mL), supplementation with 1000 IU/day of ergocalciferol was associated with improvement in physical performance as measured by timed up-and-go [71]. However, in another trial in which older women with 25OHD levels <30 ng/mL were treated with 800 IU cholecalciferol daily or 50,000 IU cholecalciferol twice-monthly to increase the 25OHD to ≥30 ng/mL or with placebo, muscle function, as measured by timed-up-and-go and sit-to-stand tests, did not improve significantly in any of the treatment arms [72]. Since the effects of vitamin D supplementation on muscle function have been mixed, a metaanalysis of 17 RCTs was performed. The results indicated that vitamin D supplements were only effective in improving muscle strength in individuals who were vitamin D deficient (as defined by serum 25OHD <25 nmol/L or <10 ng/mL) at enrollment [73]. This metaanalysis highlights the importance of selection of appropriate individuals for vitamin D supplementation.

Vitamin D and muscle in CKD

25OHD and 1,25-$(OH)_2D$ deficiency in CKD

Both 25OHD and 1,25-$(OH)_2D$ levels may decrease with declining kidney function. The kidney is the main site of conversion of 25OHD to 1,25-$(OH)_2D$. Thus as renal mass and function decrease, levels of 1,25-$(OH)_2D$ as well as 25OHD decrease in CKD. Complicating this altered milieu, several factors interfere with 1,25-$(OH)_2D$ actions in renal failure. In addition to decreased serum 1,25-$(OH)_2D$ concentrations, there is also a reduction in expression of the VDR in the parathyroid gland, which may lead to vitamin D resistance in CKD [74]. Studies in nephrectomized rats indicate there is also decreased nuclear receptor RXRs expression leading to decreased formation of the VDR/RXR complex and impaired DNA binding and transcriptional signaling. Serum FGF-23 rises early as CKD develops and increases the activity of 24-hydroxylase, which in turn hydroxylates 1,25-$(OH)_2D$ and 25OHD to inactive forms [75]. In mice with elevated serum FGF-23 levels, administering antibodies to neutralize FGF-23 led to increased 1,25-$(OH)_2D$ concentrations and also to increased grip strength and spontaneous movement [76].

In addition to deficiency and resistance to 1,25-$(OH)_2D$, there is also a high prevalence of 25OHD deficiency in individuals with CKD [77,78]. A cross-sectional study in the United States showed that the prevalence of 25OHD insufficiency (serum 25OHD, 10–30 ng/mL) was 57% and 58% among those with CKD stages 3 and 4, respectively, and the prevalence of 25OHD deficiency (serum 25OHD, <10 ng/mL) was 14% and 26%, respectively [77]. These rates of insufficiency and deficiency are considerably higher than the prevalence rates in the general population, which range from 27% to 50% according to data from the Third National Health and Nutrition Examination Survey (NHANES) [45]. The physiological mechanisms causing decreased serum 25OHD in CKD are less well established than those of 1,25-$(OH)_2D$. There is some evidence that decreased reabsorption of filtered 25OHD in the renal proximal tubule [79] and decreased production of cholecalciferol in skin of CKD patients may play a role. Loss of muscle mass and decreased physical activity that accompany CKD may contribute to 25OHD deficiency because the skeletal muscle itself is important in the storage and maintenance of 25OHD levels when the availability of vitamin D is low [80]. Higher amounts of physical activity (even indoor exercise) are also positively associated with vitamin D status [81,82]. Therefore there might be a spiral wherein low vitamin D contributes to decreased physical function and muscle mass, which decreases ability to store vitamin D, which then further reduces muscle mass.

Relative importance of 25OHD and 1,25-$(OH)_2D$ for preservation of muscle mass and function in CKD

Whether repletion of 25OHD, in addition to active 1,25-$(OH)_2D$, suppresses hyperparathyroidism, increases survival, or improves mineral metabolism in advanced, nondialyzed CKD patients or ESRD patients is controversial [83–85]. It is also unclear whether the vitamin D actions on the skeletal muscle in advanced CKD patients is dependent entirely on 1,25-$(OH)_2D$ or whether 25OHD also contributes to these processes. Although the VDR in skeletal myocytes has a 500- to 1000-fold greater affinity for 1,25-$(OH)_2D$ as compared to 25OHD, there is an approximately 500-fold higher concentration of 25OHD in skeletal muscle [86]. Investigations addressing the relative effects of 25OHD and 1,25-$(OH)_2D$ have been limited to observational studies and very small randomized trials with short durations of treatment; hence, there are insufficient data to compare the effects of 25OHD versus 1,25-$(OH)_2D$ on muscle.

Observational studies

Observational studies in advanced CKD patients and MHD patients show an inverse association between serum 25OHD concentrations and lean body mass and muscle cross-sectional area [87,88]. A study using the Korean NHANES data indicated a higher prevalence of sarcopenia in participants with CKD and 25OHD deficiency (defined as serum 25OHD <20 ng/mL) as compared to those with CKD without 25OHD deficiency [89]. MHD patients who were receiving 1,25-$(OH)_2D$ also had higher muscle strength, as measured by isokinetic strength of knee extensors and isometric strength of ankle dorsiflexors, than those not receiving 1,25-$(OH)_2D$, but there was no significant difference in physical performance as measured by gait speed, stair climb, sit-to-stand time, or get-up-and-go time [90]. However, Gordon et al. found that serum concentrations of both 25OHD and 1,25-$(OH)_2D$ were directly correlated with gait speed in patients with stages 3 and 4 CKD [87]. Boudville et al. found that serum 25OHD concentrations, but not serum 1,25-$(OH)_2D$ levels, correlated with isometric quadriceps strength in MHD patients [91].

Interventional studies

Interventional studies of supplemental 25OHD and 1,25-$(OH)_2D$ in CKD have mainly focused on the effects on hyperparathyroidism, renal osteodystrophy, and mineral metabolism. Few clinical trials have the effects on explored muscle mass or function, and the results have been conflicting. In a small clinical trial of 52 participants, Marckmann et al. treated nondialyzed advanced CKD patients and MHD patients with 40,000 IU cholecalciferol per day for 8 weeks. Compared with those treated with placebo, participants treated with cholecalciferol did not achieve significant improvement in muscle function as measured by the weight lifted by the dominant arm and sit-to-stand testing at 8 weeks [92]. Hewitt et al. completed a similar trial in 60 MHD patients with a longer treatment time of 6 months. Although baseline serum 25OHD concentrations correlated with distance in the 6-minute walk test, there were no significant changes in grip strength, elbow, hip, and knee extension/flexion strength, or functional tests, including repeated chair stand, postural stability, and 6-minute walk distance after 6 months of cholecalciferol supplements [93]. However, in another trial of 25 patients with CKD stages 3–4 and 50 chronic peritoneal dialysis patients, supplements of 50,000 IU cholecalciferol given once-weekly for 4–8 weeks resulted in a significant increase in isokinetic strength of the flexor and extensor muscles of the knee. There was no significant difference between the cholecalciferol versus placebo treatment groups in muscle function as measured by timed repeated chair standing, stair climb, or gait velocity [94]. Lack of statistical power, different durations of treatment, and publication bias are possible explanations for these conflicting results with regard to changes in muscle strength and function, although it is notable that the longer study did not report more benefits than the studies of shorter duration. It is noteworthy that none of these trials used 1,25-$(OH)_2D$ as the form of vitamin D supplementation, so it is still unclear whether 1,25-$(OH)_2D$ might be more effective at improving muscle function.

The 2020 KDOQI Clinical Practice Guidelines for Nutrition in CKD recommend vitamin D supplementation in the form of cholecalciferol or ergocalciferol in CKD stages 1–5D to correct 25OHD deficiency or insufficiency [95]. In adults with CKD with nephrotic range proteinuria, the guidelines recommend consideration of supplementation of cholecalciferol or ergocalciferol. The guidelines do not explicitly address whether supplementation with cholecalciferol, calcitriol, or a combination of both would result in benefits to muscle strength or function in CKD patients. Larger randomized trials are needed to determine whether the dosage, length of supplementation, or type of vitamin D compound will influence the effects of vitamin D on muscle strength and function. Studies from the general population have shown that high doses of vitamin D may actually increase fall risk [96], and in the CKD population, there continues to be concern regarding excess vitamin D contributing to vascular calcification [97].

Testosterone

Although the name testosterone was only coined in 1935, it has long been theorized to have benefits for improving well-being. In 1889 Brown-Sequard published results of his self-experimentation and described "rejuvenation by testicular extracts" [98]. Other physicians followed, with reports describing that testicular extracts "increased capacity of work considerably above that which would follow exercise alone." Brown-Sequard's observations may have been overstated, as modern scientists have repeated the extraction of hormones from dog testes using the Brown-Sequard method and found that his injections would have contained only approximately 100 ng of testosterone; the testicles do not store testosterone in large concentrations even though they are the site of testosterone synthesis. These scientists who could not replicate Brown-Sequard's results concluded that "the placebo effect can be powerful, even in a highly educated physician" [99]. The androgenic substance named testosterone was finally isolated from bull testes by Ernst Laqueur in 1935. Subsequently, in 1939, Adolf Butenandt and Leopold Ruzicka were awarded the Nobel Prize for the synthesis of testosterone, thus jump-starting the field of therapeutic testosterone for increasing muscle size and strength.

Mechanism of testosterone's anabolic effects on muscle

Testosterone induces muscle fiber hypertrophy by several mechanisms, tipping the balance of protein synthesis and breakdown toward net anabolism. Evidence suggests that testosterone increases protein synthesis in skeletal muscle without increasing intracellular amino acid transport by reusing amino acids generated from protein breakdown for synthesizing new protein. Testosterone may also decrease the amount of protein catabolism that occurs during fasting [100−102]. In addition, testosterone has been shown to increase the number of satellite cells, the precursor to new myocytes, in the muscle in a dose-dependent manner. Therefore testosterone can increase skeletal muscle mass not only by myofiber hypertrophy but also by increasing myoblast differentiation.

Testosterone acts directly through the androgen receptor with both genomic and nongenomic effects. Genomic effects of testosterone stimulate myogenic differentiation while inhibiting adipogenic differentiation [103]. Nongenomic effects of testosterone activate a cascade of intracellular calcium release and the Ras/MEK/ERK1/2 pathway [104]. Outside of the myoblast, motor neurons are also dependent on androgens. In castrated animals, motor neurons decrease in size [105]. But when these animals are treated with testosterone, their motor neurons increase in number [106]. Finally, in addition to exerting positive regulation on muscle growth, testosterone also inhibits the transcription of myostatin in rats [107].

Clinical trials in the general population of the effects of testosterone on muscle mass and muscle function

The use and abuse of anabolic and androgenic substances for increasing muscle size and strength was prevalent even before there were high-quality data showing their efficacy in humans. Despite the long-heralded anecdotal effects of testosterone on muscle among athletes, the scientific data on the anabolic effects of testosterone were controversial for many decades. However, starting in the late 1990s, there was a surge in clinical trials of different testosterone formulations that explored the effects on muscle mass and strength. Bhasin et al. were the first to show that testosterone injections, at supraphysiological doses, increased fat-free mass, muscle size (as measured by triceps and quadriceps area), and muscle strength (as measured by bench-press and squatting-exercise) in a linear fashion [108]. Testosterone was then also shown to increase lean mass in hypogonadal men [101,109,110], in older men with low-normal testosterone [111,112], and in men with HIV [113−115].

Although testosterone has been consistently shown to increase muscle size, whether it also improves physical function has remained more controversial. The Testosterone in Older Men with Mobility Limitations (TOM) trial was a randomized controlled trial designed to determine if testosterone gel increased lower extremity strength in men ages 65 and older. The trial was stopped early in 2009 when the data and safety monitoring board found more adverse cardiovascular events occurred in the testosterone group than in the placebo group [116]. (Cardiovascular complications of testosterone treatment will be discussed in more detail later in this chapter.) However, in 2016, Snyder et al. published results from 790 men who participated in The Testosterone Trials, a coordinated set of smaller trials that included the Sexual Function Trial, Physical Function Trial, and the Vitality Trial. In the Physical Function Trial the primary outcome was distance walked in 6 minutes, and the secondary outcome included the Physical Function score (PF-10) of the Medical Outcomes Study 36-Item Short-Form Health Survey. Although there was no significant difference in 6-minute walk distance in the cohort enrolled in the Physical Function Trial, there was a significant increase in the PF-10 score among those treated with testosterone compared with those who received placebo. When combining all testosterone trial participants, there was a significant increase in 6-minute walk distance and PF-10 score [117].

Testosterone in CKD and ESRD

Serum testosterone decreases with age and chronic illness, and the prevalence of testosterone deficiency is higher in men with ESRD (44% in a Swedish cohort) than in healthy men of similar age (5.6%−9.5%) [118,119]. The precise mechanisms leading to the disruption of the hypothalamic−pituitary−gonadal axis in patients with CKD and ESRD are still unclear. Several possible mechanisms include (1) disruption in gonadotropin-releasing hormone by the hypothalamus leading to a decreased pulsatile release of luteinizing hormone (LH) by the pituitary gland; (2) hyperprolactinemia and elevated serum LH levels from reduced renal clearance, producing a negative feedback on the hypothalamus [120]; (3) increased sensitivity in the pituitary to the negative feedback from testosterone itself [121]; and (4) testicular failure in CKD due to possible inhibitors to LH receptor signaling [122], abnormal testicular histology with impaired germinal and Leydig cell function, and low testicular volume [123].

In patients with ESRD, Carrero et al. showed that men with low serum testosterone concentrations (in the lowest tertile) had a 2.03-fold higher hazard ratio (1.24−3.31) for all-cause mortality as compared with the nonlow testosterone group (i.e., the highest and middle tertiles) [124]. As in the general population, there is evidence that serum testosterone and muscle mass are closely associated in patients with advanced CKD and ESRD; but evidence is still unclear to what extent serum testosterone affects physical function in CKD and ESRD patients. Observational studies of people with CKD and ESRD found that lower serum testosterone concentrations were associated with reduced muscle mass and fat-free mass, as estimated by bioelectrical impedance vector analysis [125], computed tomography [126], and serum creatinine (sCr) levels [124].

These observational studies have been confirmed by several small interventional trials. The first such study of androgen therapy in the dialysis population was a small 6-month randomized controlled trial of the synthetic testosterone derivative nandrolone decanoate. Patients who received nandrolone demonstrated increased lean body mass and a decrease in walk and stair-climbing time as compared with those who received placebo [127]. Subsequently, a larger 2 × 2 factorial trial of nandrolone decanoate and lower extremity resistance exercise training for 3 months was conducted in 79 MHD patients. In contrast to the earlier study, although resistance exercise training resulted in increased lower extremity strength, nandrolone treatment did not. One possible explanation for the lack of measurable change in physical function with nandrolone decanoate was the shorter duration of treatment in this study [128]. In another study in MHD patients, treatment with oxymetholone increased fat-free mass and type I muscle fiber cross-sectional area. These investigators also observed an improvement in handgrip strength and self-reported physical function scores [129].

No long-term interventional studies with androgenic agents have been conducted, but recent observational studies have examined longitudinal associations of serum testosterone with body composition and physical performance. In a retrospective longitudinal study with 440 men receiving MHD, investigators studied the change in serum testosterone concentrations, muscle mass, and physical function over 1 year [17]. Serum-free testosterone levels were associated with muscle mass (estimated by sCr and by bioelectrical impedance spectroscopy) and several measures of physical performance. In addition, lower serum-free testosterone was associated with higher odds of being frail at baseline, of becoming frail over 12 months (as defined by the Fried Frailty phenotype [130]), and of having sarcopenia. Of the frailty criteria in the Fried phenotype, serum-free testosterone concentration was specifically associated with grip strength and gait speed at baseline and over 12 months [17]. A long-term randomized clinical trial in advanced CKD and ESRD patients, similar to The Testosterone Trial, is needed to confirm the results of these observational and smaller randomized trials: that testosterone replacement increases lean body and muscle mass and may increase physical function.

Clinician guide to treating hypogonadism

Because treatment of hypogonadism is an available option that might increase muscle mass among men with advanced CKD or who are undergoing chronic dialysis, we will discuss its diagnosis and management.

Diagnosis of hypogonadism

Serum testosterone levels are highest in the morning and decrease throughout the day. More than 95% of testosterone circulates bound to sex hormone−binding globulin (SHBG), and a small proportion is weakly bound to albumin. The free testosterone is the unbound fraction, and biologically active testosterone consists of free testosterone and the proportion of testosterone that is weakly bound to albumin. Several factors affect SHBG concentrations in advanced CKD and chronic dialysis patients, including diabetes, obesity, and older age, and thus serum total testosterone may give a false estimation of biologically active testosterone at the tissue level. Bioactive testosterone is difficult and expensive to measure commercially, and there is wide variability between laboratory assays and the normal ranges. Therefore serum-free testosterone may be the best clinically available measure to estimate biological activity of testosterone in advanced CKD and chronic dialysis patients. It is noteworthy that many serum-free testosterone immunoassays are inaccurate and unreliable, and there is substantial variability of results among different assays. The gold standard is measurement of free testosterone by equilibrium dialysis and liquid chromatography/mass spectrometry [131]. However, in practice, serum-free testosterone can be estimated based on measures of total testosterone and SHBG.

Serum testosterone and SHBG measurements should be obtained in the morning from a fasting blood sample, and at least two measurements on separate days should be obtained to confirm hypogonadism. The lower limit of serum normal testosterone for the assay used determines hypogonadism; for most assays, this is around 200−400 ng/dL. Most of the limits for the normal range of serum testosterone are set by the values from healthy, nonobese young men, and there are currently no standardized age-stratified normal testosterone levels. If hypogonadism is confirmed, serum LH, follicle-stimulating hormone (FSH), and prolactin should also be measured. In advanced CKD and ESRD patients, serum LH and FSH tend to be high. However, high serum LH and FSH may also point to other primary sources of hypogonadism, such as Klinefelter syndrome or cryptorchidism, and the clinical history may help to differentiate between these causes. If serum LH and FSH are low or low normal with a serum total testosterone that is <100 ng/dL, an endocrinology evaluation is recommended to rule out pituitary adenoma as a cause of hypogonadism.

Treatment of hypogonadism

The Endocrine Society recommends against giving testosterone therapeutically to men who are planning to reproduce or who have a serum prostate-specific antigen (PSA) level >4 ng/mL or a PSA level >3 ng/mL and a high risk of prostate cancer. Other contraindications to testosterone replacement include elevated hemoglobin, thrombophilia, untreated obstructive sleep apnea (OSA), severe lower urinary tract symptoms related to benign prostatic hyperplasia, uncontrolled heart failure, or a myocardial infarction or cerebral vascular event within the previous 6 months.

Testosterone formulations

Formulations of testosterone have improved greatly over the last several decades. The most commonly used and most cost-effective formulations currently are transdermal and injectable testosterone (Table 52.2). Testosterone replacement does not have to be dose adjusted in the setting of CKD or chronic dialysis.

TABLE 52.2 Testosterone formulations available in the United States.

Testosterone formulation	Typical starting dose	Advantages	Disadvantages
Testosterone cypionate	150 mg IM every 2 weeks or 75 mg weekly	Widely available and affordable	Peak and trough concentrations in testosterone may produce fluctuations in symptoms
Testosterone gel (AndroGel, Fortesta, Vogelxo, Testim)	AndroGel: [1%: two 25 mg packets daily; 1.62%: 1 pump (20.25 mg) daily]	Less fluctuation in testosterone concentration. Less skin sensitivity than patch	Variation in absorption due to skin and environmental factors. Potential transfer from skin-to-skin contact
Testosterone Axillary Topical Solution (Axiron)	30−60 mg applied to the axilla daily	Less fluctuations in testosterone level. Less skin sensitivity than patch	Variation in absorption due to skin and environmental factors. Potential transfer from skin-to-skin contact. Expensive
Transdermal Testosterone patch (Androderm)	2−4 mg patch applied every 24 h	Less fluctuations in testosterone level. Easy to apply. Affordable	Skin irritation is common. May need multiple patches to achieve normal range
Buccal Testosterone (Striant)	30 mg applied to gums BID	Convenient. Steady testosterone levels	Gum-related adverse events. Expensive
Nasal Testosterone (Natesto)	11 mg (1 actuation per nostril) TID	Noninvasive. Less risk of unintentional transfer to others. Avoids first-pass metabolism	TID dosing. Expensive. Nasal adverse events
Oral testosterone undecanoate (Jatenzo)	237 mg BID	Bypasses first-pass metabolism	Bioavailability differs according to fat content in meals. Variable testosterone concentration
Testosterone pellets	600−1200 mg implanted subcutaneously	Sustained release for 3−6 months	Requires surgical incision

IM, Intramuscular; *TID*, three times a day; *BID*: twice a day.

Safety and monitoring

Testosterone administration is associated with erythrocytosis in a dose-dependent manner, although this may be a more beneficial effect than harmful in advanced CKD and chronic dialysis patients because of the prevalence of anemia in this population. Androgen receptor signaling is also important for the growth of prostate cancer and continues to be a concern for people receiving testosterone supplements. However, there is currently no strong evidence to suggest that testosterone administration increases the risk of prostate cancer. Testosterone increases PSA levels, and many older men may have small undiagnosed prostate cancer prior to treatment that may become clinically overt during testosterone treatment due to increased surveillance [132,133]. OSA can worsen during testosterone therapy, possibly due to depression of the hypercapnic ventilatory drive [133].

Cardiovascular events are of concern as the chronic dialysis population carries a higher risk of cardiovascular disease than the general population for these events. However, the risk of mortality and adverse cardiovascular events with testosterone use continues to be controversial because of contradictory data. Small randomized trials have demonstrated that testosterone administration decreased exercise-induced myocardial ischemia [134] and chronic stable angina [135]. Two large observational studies published by Shores et al. showed that veterans with low serum testosterone (≤250 ng/dL) had a higher hazard of all-cause mortality than those with normal serum testosterone concentrations [136]. Furthermore, those treated with testosterone had a lower risk of death compared with untreated men [137]. However, the TOM trial was discontinued due to a higher rate of cardiovascular events among participants receiving testosterone [116]. Participants in the TOM trial who had cardiovascular events also had a larger increase in their serum testosterone than those who did not [116]. Vigen et al. conducted a large observational study to examine the association between testosterone and major adverse cardiovascular events (MACE) and found that testosterone therapy was associated with a higher risk of adverse outcomes (HR 1.29; 95% CI, 1.04–1.58) [138]. Published criticisms of this study have focused on the low rate of MACE, short duration of therapy, and lack of confirmation concerning the adherence of participants to the prescribed dose of testosterone [139]. Subsequently, The Testosterone Trial did not show any difference in MACE rates between the treatment and placebo groups [117]. In men receiving chronic dialysis, Carrero et al. reported that serum testosterone concentrations were *inversely* correlated with cardiovascular-related mortality [140]. It is uncertain how the data on cardiovascular risk in the general population would translate to men with advanced CKD or ESRD. Therefore large clinical trials in this population would be needed to fully address this question.

Monitoring during testosterone replacement therapy consists of measuring serum testosterone (usually 1 month after initiation), a hemoglobin or hematocrit level (usually around 3 months), and a yearly serum PSA level. Serum for testosterone measurement during treatment can be obtained at any time, since the timing and formulation of testosterone administration determines the serum levels more than the natural circadian rhythm. Clinicians should aim to maintain serum testosterone in the midnormal range for healthy young men. If the PSA increases by more than 1.4 ng/mL from the baseline concentration or rises to a level above 4.0 ng/mL, a urological consultation is warranted.

Future directions

The future of androgenic therapy will probably include further development of selective androgen receptor modulators (SARMs) and clinical trials to test these agents. SARMs are an attractive way to separate the androgenic properties from the anabolic properties of androgenic substances. The mechanism by which SARMs can achieve specificity of action in tissues remains poorly understood. SARMs are formed by adding or substituting chemical groups to testosterone. One potential way to change the specificity of testosterone is by the addition of alkyl groups to the testosterone compound which then changes how the resulting androgen compound interacts with 5 α-reductase. The enzyme 5 α-reductase, which is highly expressed in the prostate gland but not in skeletal muscle, converts testosterone to dihydrotestosterone, which is a more potent androgen in the prostate. Therefore molecules that make the androgenic compound less susceptible to 5 α-reductase can retain anabolic activity in the muscle but have lower androgenic activity in the prostate [141]. It is also thought that the chemical scaffolds used in SARMs could induce conformational changes in the androgen receptor leading to its association with different coactivators which could then result in tissue-specific gene regulation [141]. In preclinical trials, SARMs have been shown to increase the weight of levator ani muscles in rats [142]. The development of SARMs for human use has been slow. Several compounds have been abandoned due to toxicity or lack of efficacy, but considerable effort is underway to improve the safety and efficacy of these compounds. The drug that has progressed farthest in clinical trials is enobosarm (Gtx Inc), which was shown to increase lean body mass and physical function as measured by stair climbing in healthy elderly men and postmenopausal women in phase II trials [143]. Phase III trials in several cancer populations are ongoing.

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CHAPTER

53

Nonnutritional and nonhormonal methods to affect muscle strength and physical performance

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In patients with end-stage renal disease (ESRD), regular physical exercise can be considered a cornerstone for the treatment of uremic myopathy and possibly concomitant cardiovascular disturbances [1–3]. Resistance training in these patients is reported to increase strength, functional capacity, and muscle size [4–6]. Endurance training increases functional capacity, also referred to as aerobic capacity; in some studies, endurance training is reported to ameliorate hypertension, reduce sympathetic overactivity, decrease the incidence of arrhythmias and heart rate variability, and improve health-related quality of life [7–9]. The combination of resistance and endurance training appears to be particularly effective [10–12]. Physical exercise also may exert antiinflammatory effects with lowering of the serum inflammatory markers, C-reactive protein and interleukin 6 [13,14]. However, many patients with ESRD are unable or unwilling to perform conventional exercise programs [15]. Two alternative methods for attaining the benefits of active physical exercise are neuromuscular electrical stimulation (NMES) and whole-body vibration (WBV) training.

Neuromuscular electrical stimulation

NMES induces muscle contractions by electrical impulses that are delivered to the muscles through electrodes placed on the skin. NMES is frequently used for strength training in healthy subjects and athletes. In animal models and human studies, increased muscle mass and muscle function have been achieved with NMES [16–18]. Strong evidence for improving impaired muscle function by NMES was observed in various chronic diseases, including heart failure [19,20], chronic obstructive pulmonary disease (COPD) [21], spinal cord injury [22], critically ill patients with septicemia [23], and sedentary elderly subjects [24].

The effects of NMES training on muscle function in ESRD patients were investigated in small groups of maintenance hemodialysis (MHD) patients and in one group of chronic peritoneal dialysis patients [25–32]. The results of 2–3 months of NMES training showed increased strength of the leg extensors, which was associated with augmented quadriceps muscle area [29,30] and enhanced walk distance [29]. In two trials in chronic dialysis patients, NMES training improved maximal exercise capacity [31,32] and enhanced the anaerobic threshold (VO2 AT), which is a measure of aerobic capacity with important correlations with physical conditioning and health [33]. Arterial stiffness, assessed by cardio-ankle vascular index and impaired endothelial function, was not influenced by NMES [29,31,32].

In comparative studies of NMES and cycling exercise during hemodialysis, the benefits on physical exercise capacity were similar with both treatments [20,30]. NMES treatment also improved pulmonary function in severely disabled patients with COPD [21]. In healthy

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subjects an enhancement of whole-body glucose uptake was observed after treatment with NMES [34]. Routine blood chemistry measurements (creatinine, uric acid, hemoglobin, glucose, HDL- and LDL-cholesterol, triglycerides, and electrolytes) were not affected in several NMES studies. However, in one trial, a lowering of plasma urea was observed in both the NMES-treated and the active exercising groups [20].

Many parameters of quality of life, assessed by the short form of the Kidney Disease Quality of Life (KDQOL) questionnaire (SF-36), were improved after NMES treatment [26,32]. In particular, improvements in mental function and in some aspects of physical function were observed. The effects were similar to data published after active physical exercise training in patients with ESRD [7].

Altogether, these studies demonstrate striking effects of NMES on muscle strength of the lower limbs, functional capacity [6-minute walk test (6-MWT)], and measures of quality of life. The limitations of these studies are the small numbers of participants and the short intervention times. Therefore further investigations will be necessary with more participants and a longer follow-up to establish the potential benefits of NMES for ESRD.

Effects of electrotherapy for pain in end-stage renal disease patients

Pain is a potential contributor to skeletal muscle wasting. Persistent pain may induce adverse physical, mental, and social consequences, including sleep disorders, anxiety, depression, and reduced daily physical activity [35,36], which favors the development of muscle wasting [37]. Peripheral polyneuropathy may also contribute to muscle wasting [38]. Approximately 50% of MHD patients suffer from chronic pain [39]. However, three-quarters of these patients are not effectively treated [40], in part, due to the polypharmacy taken by MHD patients and the frequent drug-related side effects of many analgesic agents that occur in ESRD [41,42].

Potential nonpharmacological strategies for chronic pain treatment in ESRD patients include physical exercise [43], psychiatric or spiritual counseling [44], meditation, relaxation techniques and hypnosis [45], as well as yoga-based programs [46]. The following forms of electrotherapy are treatments of interest that might have a role in pain management: transcutaneous nerve stimulation (TENS [47]), the so-called high-tone external muscle stimulation (HTEMS [48]), percutaneous nerve stimulation [49], and spinal cord stimulation [50].

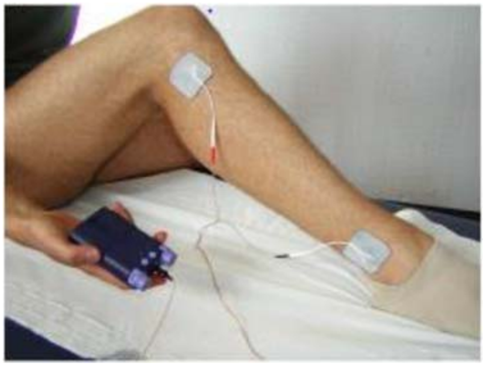

FIGURE 53.1 Placement of TENS electrodes for the treatment of neuropathic pain. *TENS*, Transcutaneous nerve stimulation.

Transcutaneous nerve stimulation

TENS is the most commonly used form of nonpharmacological pain treatment. It consists of a battery-powered portable electric unit with electrodes applied to the skin delivering electrical impulses to the underlying nerve fibers (Fig. 53.1). The frequency modes of TENS are high frequency ($HF > 50$ Hz), low frequency ($LF < 10$ Hz), and variable frequency [51]. In a placebo-controlled randomized study in diabetic patients, TENS treatment significantly improved the painful symptoms of distal symmetric polyneuropathy [47], pain associated with rheumatoid arthritis [52], and pain following various surgical procedures [53]. However, TENS treatment for lower back pain is not recommended [54]. Preliminary data indicate that TENS might also be effective for treating cancer-related pain [55]. A recent randomized pilot trial in individuals with dementia indicated that treatment with TENS appeared to raise the pain threshold and improve functional capacity [56]. Moreover, TENS therapy may be useful for patients with peripheral arterial disease and intermittent claudication [57].

High-tone external muscle stimulation

Another option for pain treatment is referred to as HTEMS or high-frequency external muscle stimulation (Fig. 53.2). Here, continuously the initial frequency of 4096 Hz is increased up to 32,768 Hz within 3 seconds, remaining at this maximum for further 3 seconds and then downmodulated to 4096 Hz again. This allows for a more efficient stimulation of the muscles. In a short-term comparative investigation conducted for three consecutive days in patients with symptomatic diabetic peripheral polyneuropathy, HTEMS alleviated pain significantly more effectively than did TENS [48]. Daily treatment with HTEMS for 6 weeks in type 2 diabetic patients was followed by lowering of body

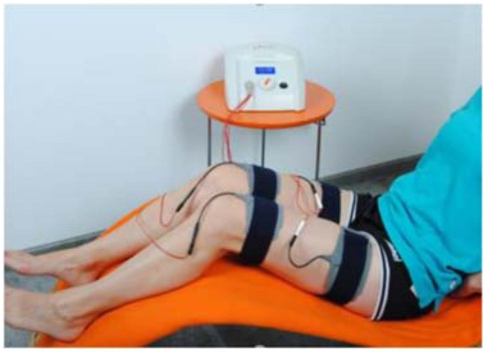

FIGURE 53.2 Placement of HTEMS electrodes for the treatment of pain. *HTEMS*, High-tone external muscle stimulation.

weight and significant improvement in diabetic control. Serum levels of some measures of inflammation also tended to decrease [58].

The effect of HTEMS on symptomatic uremic and diabetic peripheral polyneuropathy was investigated in an uncontrolled multicenter study of 40 MHD patients [59]. Treatment was performed for 1 hour during hemodialysis three times per week. After 12 weeks of HTEMS, there was a significant amelioration of tingling, burning, pain, numbness, and increased duration of sleep as compared to baseline values. These positive effects persisted for more than 1 year with exception of the improvement in sleep duration [60]. The blood chemical values, including C-reactive protein were not altered [59]. In a further uncontrolled investigation of health-related quality of life using the SF-36 scales in 25 MHD patients, 12 weeks of HTEMS treatment resulted in a statistically significant improvement in the subscales of physical role functioning [61]. The beneficial effects of HTEMS on painful uremic polyneuropathy were extended by Strempska et al. [62], who showed that the amelioration of pain was associated with a significant improvement in motor nerve conduction velocity. However, in none of the studies of TENS and HTEMS, their effects on muscle dysfunction were investigated.

Since HTEMS was shown to acutely increase renal blood flow in healthy subjects [63], its effect on the clinical course of patients with acute kidney injury (AKI stage 3) was studied in 34 patients with AKI who were randomized to either receive or not receive treatments with HTEMS. The daily electrical HTEMS therapy was associated with a significant shortening of the clinical course of AKI [64]. Moreover, HTEMS therapy was associated with a significant reduction in the serum levels of nitric oxide (NO), asymmetric-dimethylarginine, and endothelin-1 in the AKI patients [65]. Interestingly, HTEMS treatment in diabetic patients was also associated with an increase in vascular endothelial growth factor 2 in circulating hematopoietic stem cells and a decline in plasma catecholamines [66].

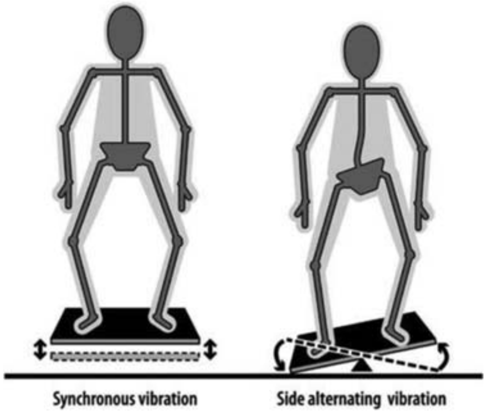

FIGURE 53.3 Forms of vibration trainings. Direction of vibration movement in synchronous and in side-alternating vibration. Source*: Reproduced with permission from Rauch F, Sievanen H, Boonen S, Cardinale M, Degens H, Felsenberg D, et al.; International Society of Musculoskeletal and Neuronal Interactions. Reporting whole-body vibration intervention studies: recommendations of the International Society of Musculoskeletal and Neuronal Interactions. J Musculoskelet Neuronal Interact 2010;10(3):193–8, with permission.*

In general, electrotherapy with NMES, TENS, and HTEMS are well tolerated, but these treatments should be avoided in patients with cardiac pacemakers, implantable cardioverter-defibrillators, or other indwelling electrical stimulators.

Whole-body vibration training

WBV exercise is another intervention modality to improve impaired muscle function [67]. WBV training is performed on motor-driven vibrating plates, which cause changes in the length of the muscle-tendon complex that evokes reflexive muscle contractions (Fig. 53.3) [68,69]. The electromyographic activity of the muscles is directly correlated with the frequency of the applied vibrations [70,71]. There are basically two different forms of WBV devices: in the synchronous operating platforms, both feet are moved up and down in parallel, while in the side alternating vibration one foot is moving up, while the other one is moving down inducing a sinusoidal vibration. The side-alternating plates are considered to act in a more physiological manner.

In the 1970s, Russian scientists used biomechanical stimulation of single muscles for cosmonauts to promote recovery after long flights. The first publication about WBV with a side-alternating device appeared in 1998 [72]. In a randomized controlled study, this training significantly improved the jumping performance. Later, WBV became increasingly popular among exercising adults and trained athletes who combine WBV with physical exercise training [73].

WBV has been shown to enhance muscle activity, force, power, balancing ability, and flexibility [74–76]. It enhances peripheral circulation [77,78] and reduces arterial stiffness, while blood pressure and heart rate did not change in most studies [79–81]. WBV was associated with improved glycemic control in type 2 diabetic patients [82]. During long-term bed rest, WBV training was also associated with the reduction of muscle and bone loss [83]. Moreover improvement in osteoporosis [84] and functional deficits of sedentary elderly subjects were shown [67,68,84]. Inconsistent results with WBV were reported in Parkinson's disease [85] and in multiple sclerosis [86]. Moderate improvement was achieved in stroke patients [87] and in patients with COPD [88]. Moreover, WBV may exert positive effects on chronic musculoskeletal pain [89] and the impaired functional performance of jump height and semitandem stance, which occurs during high-dose chemotherapy of patients with hematological malignancies [90]. The first studies with WBV in MHD patients were performed by Seefried et al. [91] where 14 participants used the side-alternating vibratory Galileo platform three times weekly before hemodialysis treatment for 3 months. The results showed a statistically significant improvement of the primary outcome, the Short Physical Performance Battery (SPPB), which is the sum of the scores of the Static Balance Test, the Gait Speed Test (GST), and the timed 5-Chair Rise Tests (CRTs). The training response was most pronounced in the subgroup in the lowest tertile for the SPPB score at baseline (Fig. 53.4). These findings are similar to results in MHD patients who were participating in an active exercise program [92].

The individual components of the SPPB showed only marginal changes for the GST, but substantial improvements for the static balance testing and the timed 5-CRTs. The secondary endpoints revealed slight-to-moderate improvements in the Timed-Up and Go test, the distance attained in the 6-MWT, and in the jumping performance.

There was a mild, nonsignificant decrease in the systolic and diastolic blood pressure, which is in line with investigations of WBV in elderly subjects [68] and in overweight women [93,94]. Moreover, an increase in blood velocity and a decrease of arterial stiffness have been reported in people without kidney failure [80,81,95]. In the long run, it is possible that WBV may improve cardiovascular fitness [96].

Similar to active exercise [97], WBV training exerts antiinflammatory effects. In the study of Seefried et al. in MHD patients [91], a significant decline in white cell count was observed, while mean serum high-sensitive C-reactive protein decreased moderately but insignificantly. The WBV training was well tolerated. Patient-reported outcomes revealed a significant improvement of physical performance capability and mood.

The effects of WBV in 49 MHD patients were also investigated by Doyle et al. [98] in an uncontrolled trial using a vertical vibration platform. After an 8-week training period (three sessions for 3 minutes each per week), there was a significant improvement of the 60-second sit-to-stand test and an insignificant improvement of the Tinetti balance score. The quality of life assessment with SF-36 revealed significant improvement in two domains. Almost half of the patients dropped the study for reasons mainly unrelated to the training itself. According to the authors, treatment with WBV was well accepted by the patients; only one participant dropped out due to nausea after WBV.

For the prevention of falls, in particular in the elderly, the rapid force development at the beginning of muscle contraction is of fundamental importance. In advanced CKD patients the reaction time before rapid, forceful muscle contraction is considerably longer than

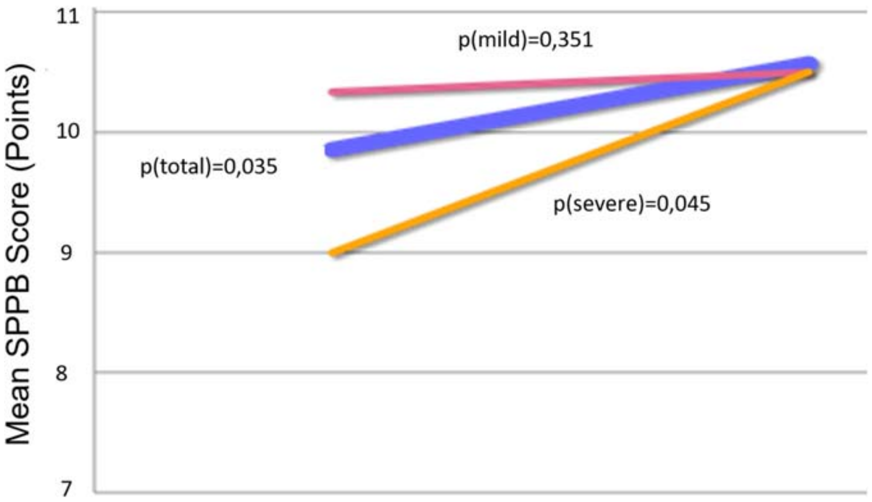

FIGURE 53.4 Effect of WBV on the SPPB. Blue: significant increase of the whole group. Yellow: best results in the tertile with the most severe physical impairment. Red: results of the tertile with the least (only minor) physical impairment. *SPPB*, Short Physical Performance Battery; *WBV*, whole-body vibration. Source*: Reproduced with permission of Seefried L, Genest F, Luksche N, Schneider M, Fazeli G, Brandl M, et al. Efficacy and safety of whole-body vibration in maintenance hemodialysis patients – a pilot study. J Musculoskelet Neuronal Interact 2017; 17(4):268–74.*

that of controls. In order to examine whether WBV might reduce the reaction time until rapid or explosive force is initiated, Fuzari et al. conducted a randomized, controlled trial in 14 hemodialysis patients [99] and demonstrated that WBV improved the reduced explosive force of knee extensor muscles. In another randomized controlled study in 16 MHD patients by Fuzari et al. [100], the effect of WBV on muscle power and mass was studied. After a 12-week training period (two WBV sessions per week) using a vertical vibration platform, a significant improvement of the maximum voluntary isometric contraction of the knee extensors was observed, while the thickness of the quadriceps muscle did not change. The walking capacity (6-MWT) and static balance increased insignificantly. Health-related quality of life (KDQOL) was not ameliorated.

In summary the few published studies of WBV training in ESRD patients suggest that this intervention may improve the impaired muscle strength of the lower legs, physical performance, and potentially some parameters of quality of life. These results are consistent with previous studies of WBV training in various other chronic diseases. Major limitations of the trials in MHD patients are the small number of participants, the short duration of the studies and, often, the lack of control groups. Therefore long-term randomized, prospective controlled trials with larger patient groups are needed to confirm the results of these studies.

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4th Edition

Nutritional Management of Renal Disease

Edited by
Joel D. Kopple
Shaul G. Massry
Kamyar Kalantar-Zadeh
Denis Fouque

Nutritional Management of Renal Disease, 4th Edition offers in-depth reviews of the metabolic and nutritional disorders prevalent in patients with renal disease and serves as an in-depth reference source concerning nutrition and kidney disease. This classic translational reference provides correct diagnosis—and therefore correct treatment—of metabolic and nutritional disorders in acute kidney injury, chronic kidney disease, kidney failure, dialysis and kidney transplantation. Nephrologists, diabetologists, endocrinologists, dieticians, and nutritionists depend on a strong understanding of the molecular basis for the disease. This fourth edition includes thorough new case reports, offering expert advice on how to use the latest research and clinical findings in counseling patients about dietary and lifestyle options. Readers gain insight into which treatments, medications, and diets to use based on the history, progression, and genetic makeup of a patient.

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